NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 349

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TWO PENTACHLOROPHENOL TECHNICAL-GRADE MIXTURES

(CAS NO. 87-86-5)

IN B6C3F$_1$ MICE

(FEED STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TWO PENTACHLOROPHENOL TECHNICAL-GRADE MIXTURES

(CAS NO. 87-86-5)

IN B6C3F$_1$ MICE

(FEED STUDIES)

E.E. McConnell, D.V.M., Chemical Manager

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

March 1989

NTP TR 349

NIH Publication No. 89-2804

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

NOTE TO THE READER

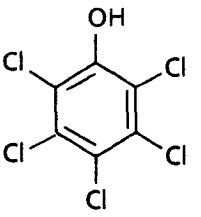
This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

CONTENTS

APPENDIXES



PENTACHLOROPHENOL

CAS No. 87-86-5

C_6HOCl_5 Molecular weight 266.3

Synonyms or common names: chlorophen; PCP; penchlorol; penta; pentachlorofenol; pentachlorofenolo; pentachlorphenol; 2,3,4,5,6-pentachlorophenol

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

ABSTRACT

Toxicology studies of pentachlorophenol, a biocide used primarily as a wood preservative, were conducted by feeding diets containing a technical-grade composite, Dowicide EC-7 (a technical-grade formulation), or pure pentachlorophenol to groups of B6C3F$_1$ mice for 30 days. These three grades plus another commercial grade of pentachlorophenol (DP-2) were used in 6-month studies. These studies were followed by 2-year carcinogenicity studies of technical-grade pentachlorophenol and of Dowicide EC-7 in feed. Genetic toxicology studies were conducted in *Salmonella typhimurium* and in Chinese hamster ovary (CHO) cells.

Thirty-Day and Six-Month Studies: Groups of 19 male mice and 5-15 female mice were fed diets containing 0, 20, 100, 500, 2,500, or 12,500 ppm technical-grade pentachlorophenol, Dowicide EC-7, or pure pentachlorophenol for 30 consecutive days. Necropsies and histopathologic examinations were performed on all animals. Selected organs were weighed. Supplemental analyses included hematology, serum chemistry, urinalysis, immunology, and hepatic enzyme induction. Compound-related deaths were observed at the highest dose (12,500 ppm) with all three materials and at 2,500 ppm with EC-7 and pure pentachlorophenol (males only). Decreases in body weight gain were also observed in the groups in which deaths occurred. Diffuse centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis of the liver were compound-related lesions observed in all groups that received pure pentachlorophenol, technical-grade pentachlorophenol, or EC-7 at 500 ppm and above. Serum enzymes associated with liver injury were increased.

In the 6-month studies, groups of 10 male and 10 female mice were given diets containing the various grades of pentachlorophenol at the following dietary concentrations: 200, 600, or 1,800 ppm technical-grade pentachlorophenol; 200, 600, or 1,200 ppm DP-2 (not used in the 30-day studies); 200, 600, or 1,200 ppm EC-7; or 200, 500, or 1,500 ppm pure pentachlorophenol for 26-27 weeks. Common control groups of 10 male and 10 female mice were fed control diets. Additional groups of male mice were examined for behavioral, histopathologic, clinical pathology, biochemical, and immunologic effects.

All mice exposed at the highest dose of technical-grade pentachlorophenol died, as did 2/10 male mice exposed at the highest dose of DP-2. No deaths were observed in mice exposed to EC-7 or pure pentachlorophenol. Markedly lower final body weights were observed in the high dose groups only (all grades of pentachlorophenol). No chemical-related clinical signs were observed at sublethal doses. No major behavioral changes were observed after 5 weeks' exposure, but increased motor activity and heightened startle responses were present at the end of the study in female mice exposed to all four grades of pentachlorophenol. All grades of pentachlorophenol caused increases in serum enzymes associated with liver injury. All grades of pentachlorophenol also resulted in a dose-related induction of aryl hydrocarbon hydroxylase and an increase in cytochrome P450. However, the technical grade was a more powerful inducer than the other grades of pentachlorophenol. Pure pentachlorophenol had no effect on humoral or cell-mediated immunity. However, DP-2 and particularly technical-grade pentachlorophenol depressed humoral immune function. A dose-related increase in liver weight was observed in mice exposed to all grades of pentachlorophenol. A dose-related increase in spleen weight was observed in male mice exposed to all grades of pentachlorophenol; a decrease in spleen weight was observed in female mice exposed to all grades of pentachlorophenol except pure.

After 6 months' exposure, histopathologic examination consistently revealed effects in the liver and urinary bladder. The liver lesions were present at all doses with all four grades of pentachlorophenol but were less severe at comparable doses in the mice exposed to pure pentachlorophenol; they consisted of hepatocellular karyomegaly, cytomegaly, and degeneration. The changes in the urinary bladder consisted of a brown granular pigment in the cells of the surface epithelium. No inflammatory or proliferative response was associated with the pigment.

Based primarily on the liver lesions observed in the 6-month studies, diets chosen for the 2-year studies contained 0, 100 or 200 ppm technical-grade pentachlorophenol or 0, 100, 200, or 600 ppm EC-7, fed to groups of 50 male and 50 female mice. DP-2 and pure pentachlorophenol were not chosen for the 2-year studies because of economic considerations and because the clinicopathologic syndrome observed in the 6-month studies was similar to that observed with EC-7.

Body Weights and Survival in the Two-Year Studies: Mean body weights of mice exposed to technical-grade pentachlorophenol and EC-7 were comparable to those of controls until weeks 36-82. Thereafter, a 4%-22% dose-related decrease was observed in the mid and high dose mice exposed to EC-7 and in high dose mice exposed to technical-grade pentachlorophenol. Females were more affected than males. Feed consumption by exposed mice was similar to that by controls. The average daily doses of technical-grade pentachlorophenol were approximately 17-18 or 35 mg/kg compared with 17-18, 34-37, or 114-118 mg/kg of EC-7. Survival of mice did not appear to be affected by exposure to either technical-grade pentachlorophenol or EC-7 at the doses used in these studies.

Neoplastic and Nonneoplastic Effects in the Two-Year Studies: The incidences of hepatocellular adenomas and carcinomas were increased (dose related) in male and female mice exposed to either technical-grade pentachlorophenol or EC-7, although the increase was less marked in females exposed to technical-grade pentachlorophenol (adenomas or carcinomas, combined: technical-grade: male--control, 7/32, 22%; low dose, 26/47, 55%; high dose, 37/48, 77%; female--3/33, 9%; 9/49, 18%; 9/50, 18%; EC-7: male--control, 6/35, 17%; low dose, 19/48, 40%; mid dose, 21/48, 44%; high dose, 34/49, 69%; female--1/34, 3%; 4/50, 8%; 6/49, 12%; 31/48, 65%).

The incidences of pheochromocytomas in male mice were significantly greater than those in controls for both technical-grade pentachlorophenol (0/31; 10/45, 22%; 23/45, 51%) and EC-7 (1/34, 3%; 4/48, 8%; 21/48, 44%; 45/49, 92%). These neoplasms were also increased in female mice exposed to EC-7 at the highest dose (0/35; 2/49, 4%; 2/46, 4%; 38/49, 78%) but not in those exposed to technical-grade pentachlorophenol (2/33, 6%; 2/48, 4%; 1/49, 2%). Hyperplasia of the adrenal medulla was observed at increased incidences in mice that received either technical-grade pentachlorophenol (male: 1/31;

10/45; female: 0/33; 4/48; 2/49) or EC-7 (male: 1/34; 19/48; 13/48; 1/49; female: 2/35; 1/49; 5/46; 17/49).

The incidences of hemangiosarcomas in the spleen and/or liver were significantly greater than those in controls for high dose female mice that received technical-grade pentachlorophenol (0/35; 3/50, 6%; 6/50, 12%) or EC-7 (0/35; 1/50, 2%; 3/50, 6%; 8/49, 16%).

Compound-related nonneoplastic lesions occurred in the liver, spleen, and nose in mice exposed to either technical-grade pentachlorophenol or EC-7. The lesions in the liver included dose-related increased incidences of clear cell foci, chronic active inflammation, pigmentation, necrosis, cytomegaly, proliferation of hematopoietic cells, and bile duct hyperplasia. Increased amounts of extramedullary hematopoiesis of the splenic red pulp were observed at increased incidences in dosed male and high dose female mice that received technical-grade pentachlorophenol (male: 5/30; 15/23; 18/46; female: 2/33; 4/13; 11/47). Acute focal inflammation of the nasal mucosa and focal metaplasia of the olfactory epithelium were observed at increased incidences in high dose mice that received EC-7 (inflammation--male: 4/35; 1/13; 3/16; 47/49; female: 0/35; 0/14; 2/5; 46/48; focal metaplasia--male: 2/35; 1/13; 2/16; 46/49; female: 1/35; 0/14; 2/5; 45/48) but not in mice exposed to technical-grade pentachlorophenol.

Genetic Toxicology: Pentachlorophenol (91.6% pure; equivalent in purity to the technical-grade pentachlorophenol used in the toxicology studies) was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in the presence or absence of exogenous metabolic activation (S9). In cytogenetic studies with cultured CHO cells, pentachlorophenol produced an increase in chromosomal aberrations in the presence but not the absence of S9 metabolic activation; conversely, sister chromatid exchanges (SCEs) were induced only in the absence of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of pentachlorophenol have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** for male $B6C3F_1$ mice fed diets containing technical-grade pentachlorophenol, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms. There was *some evidence of carcinogenic activity* for female $B6C3F_1$ mice exposed to technical-grade pentachlorophenol, as shown by increased incidences of hemangiosarcomas and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* for male $B6C3F_1$ mice exposed to pentachlorophenol, EC-7, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* for female $B6C3F_1$ mice exposed to pentachlorophenol, EC-7, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and hemangiosarcomas.

Chemically related increased incidences of nonneoplastic lesions in mice of each sex included hepatocellular cytomegaly, necrosis, inflammation, pigmentation, and clear cell foci and intrahepatic bile duct hyperplasia.

---

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF PENTACHLOROPHENOL

Technical Grade		Dowicide EC-7	
Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
0, 100, or 200 ppm technical-grade pentachlorophenol	0, 100, or 200 ppm technical-grade pentachlorophenol	0, 100, 200, or 600 ppm pentachlorophenol, Dowicide EC-7	0, 100, 200, or 600 ppm pentachlorophenol, Dowicide EC-7
Survival rates in the 2-year study			
12/35; 24/50; 22/50	29/35; 41/50; 32/50	25/35; 28/50; 29/50; 35/50	29/35; 28/50; 38/50; 39/50
Body weights in the 2-year study			
Dosed and control comparable	High dose lower than controls	High dose lower than controls	Mid and high dose lower than controls
Nonneoplastic effects			
Clear cell foci, chronic active inflammation, pigmentation, necrosis, and cytomegaly of the liver	Clear cell foci, chronic active inflammation, pigmentation, necrosis, and cytomegaly of the liver	Clear cell foci, chronic active inflammation, pigmentation, necrosis, and cytomegaly of the liver	Clear cell foci, chronic active inflammation, pigmentation, necrosis, and cytomegaly of the liver. Inflammation of nasal mucosa and metaplasia of olfactory epithelium
Neoplastic effects			
Hepatocellular adenomas or carcinomas (combined) (7/32; 26/47; 37/48); adrenal medullary pheochromocytomas (0/31; 10/45; 23/45)	Hepatocellular adenomas or carcinomas (combined) (3/33; 9/49; 9/50); hemangiosarcomas (0/35; 3/50; 6/50)	Hepatocellular adenomas or carcinomas (combined) (6/35; 19/48; 21/48; 34/49); adrenal medullary pheochromocytomas (1/34; 4/48; 21/48; 45/49)	Hepatocellular adenomas or carcinomas (combined) (1/34; 4/50; 6/49; 31/48); adrenal medullary pheochromocytomas (0/35; 2/49; 2/46; 38/49); hemangiosarcomas (0/35; 1/50; 3/50; 8/49)
Level of evidence of carcinogenic activity			
Clear evidence	Some evidence	Clear evidence	Clear evidence

Genetic toxicology (conducted with technical-grade pentachlorophenol)

S. typhimurium	CHO Cells in Vitro	
(gene mutation)	SCE	Aberration
Negative with and without S9	Positive without S9; negative with S9	Negative without S9; positive with S9

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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. 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 because of major flaws cannot be evaluated ("Inadequate Study") These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports 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 quintet is selected to describe the findings These categories refer to the strength of the experimental evidence and not to either 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 This 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

- The 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 incidences 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);
- The presence or absence of dose relationships,
- The statistical significance of the observed tumor increase;
- The 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

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms, however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Pentachlorophenol is based on 6-month studies that began in June 1980 and ended in December 1980 and on 2-year studies that began in April 1982 and ended in May 1984 at Battelle Columbus Laboratories (Columbus, Ohio).

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

E.E. McConnell, D.V.M., Chemical Manager

John Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.

(Discipline Leaders and Principal Contributors)

Jack Bishop, Ph.D.
Douglas W. Bristol, Ph.D.
R. Chhabra, Ph.D.
C.W. Jameson, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Douglas Walters, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Technical-Grade Pentachlorophenol on 7/17/86)

Roger Alison, B.V.Sc., M.R.C.V.S. (Chair) (NTP)
Roger Brown, D.V.M. (Experimental Pathology Laboratories, Inc.)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Jerry M. Franz, V.M.D. (Rohm and Haas)
Robert Maronpot, D.V.M. (NTP)
Steven Stefanski, D.V.M. (NTP)
Frank Voelker, D.V.M. Pathology Associates, Inc.

(Evaluated Slides and Prepared Pathology Report for Pentachlorophenol, Dowicide EC-7, on 7/17/86)

Frank Voelker, D.V.M. (Chair) Pathology Associates, Inc.
Roger Brown, D.V.M. (Experimental Pathology Laboratories, Inc.)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Robert Maronpot, D.V.M. (NTP)
Steven Stefanski, D.V.M. (NTP)

Principal Contributors at Battelle Columbus Laboratories
(Conducted Studies and Evaluated Tissues)

A. Peters, D.V.M.
R. Persing, D.V.M.
M. Chang, Ph.D.
A. Killmeyer, B.S.

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Provided Pathology Quality Assurance)

J. Gauchat
Roger Brown, D.V.M.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.
Naomi Levy, B.A.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on pentachlorophenol on April 18, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D. (Chair)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

Michael A. Gallo, Ph.D.
Associate Professor, Director of Toxicology
Department of Environmental and Community Medicine, UMDNJ - Rutgers Medical School
Piscataway, New Jersey

Frederica Perera, Dr. P.H.*
Division of Environmental Sciences
School of Public Health
Columbia University
New York, New York

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D. (Principal Reviewer)
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderley Park, England

Charles C. Capen, D.V.M., Ph.D.
Department of Veterinary Pathobiology
Ohio State University
Columbus, Ohio

Vernon M. Chinchilli, Ph.D.
Department of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

Kim Hooper, Ph.D. (Principal Reviewer)
Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

Donald H. Hughes, Ph.D.
Scientific Coordinator, Regulatory Services Division, The Procter and Gamble Company
Cincinnati, Ohio

William Lijinsky, Ph.D. (Principal Reviewer)
Director, Chemical Carcinogenesis
Frederick Cancer Research Facility
Frederick, Maryland

Franklin E. Mirer, Ph.D.*
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Andrew Sivak, Ph.D.
Vice President, Biomedical Science
Arthur D. Little, Inc.
Cambridge, Massachusetts

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF TWO PENTACHLOROPHENOL TECHNICAL MIXTURES

On April 18, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of pentachlorophenol 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, North Carolina.

Dr. E.E. McConnell, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male mice exposed to technical-grade pentachlorophenol, some evidence of carcinogenic activity for female mice exposed to technical-grade pentachlorophenol, clear evidence of carcinogenic activity for male and female mice exposed to pentachlorophenol, EC-7). Chemically related increased incidences of nonneoplastic lesions included hepatocellular cytomegaly, necrosis, inflammation, pigmentation, and clear cell foci and intrahepatic bile duct hyperplasia.

Dr. Hooper, a principal reviewer, agreed with the conclusions. From the information given about previous studies, he questioned whether pentachlorophenol has been adequately studied for carcinogenicity in rats and asked for clarification. Dr. McConnell said that the chemical was important enough to consider conducting NTP studies in rats. Dr. J. Huff, NIEHS, indicated that previous studies in Sprague Dawley rats were less than adequate for negative studies, since group sizes were small and since the doses used could likely have been higher. Dr. Hooper commented that results from previous carcinogenesis studies, as well as those in the present studies, did not support an important role for the impurities of pentachlorophenol, chlorinated dibenzodioxins and dibenzofurans, in the carcinogenic effects observed in mice.

Dr. Ashby, the second principal reviewer, agreed with the conclusions. He cautioned that not too much weight be given to the earlier non-NTP rat studies that were negative for carcinogenicity. Since both chemicals were mixtures, Dr. Ashby thought that giving just the pentachlorophenol structure did not acknowledge the possible contribution of the contaminants [see Table 3, page 27]. He speculated that the tumors were caused by a nongenotoxic mechanism but suggested that in vivo data would be useful.

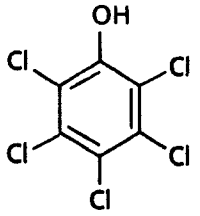
Dr. Lijinsky, the third principal reviewer, agreed with the conclusions. He concurred that the impurities played little part in causation of liver tumors; however, he thought they may have contributed to development of hemangiosarcomas of the liver and spleen. Dr. McConnell responded that the marked increases in bile duct hyperplasia, as well as the induction of cytochrome P450 enzymes, were characteristic effects of the impurities. He acknowledged that the possible role of the impurities in tumor induction was more complicated but thought they did influence liver tumor induction. Dr. McConnell presented new comparative dose data, to be added to the Report, which compared liver tumor rates in male mice exposed to pentachlorophenol containing one impurity, hexachlorodibenzodioxin, with liver tumor rates at similar doses in the NCI bioassay of this dioxin [see Figure 13, page 98].

More discussion followed on the impurities and their contributions to the carcinogenic effects compared with those of pentachlorophenol. There was consensus that it was appropriate to use the commercial samples in the studies, since humans are exposed to these. Dr. B. Schwetz, NIEHS, warned against overinterpreting the role of the impurities, noting that the studies were not optimally designed for this purpose. Further, there are contaminants other than hexachlorodibenzodioxin for which data are not available.

Dr. Hooper moved that the Technical Report on pentachlorophenol be accepted with the revisions discussed and with the conclusions as written for male mice (both technical grade and EC-7), clear evidence of carcinogenic activity, for female mice (technical grade), some evidence of carcinogenic activity, and for female mice (EC-7), clear evidence of carcinogenic activity. Dr. Lijinsky seconded the motion, which was approved unanimously with nine votes.

I. INTRODUCTION

I. INTRODUCTION



PENTACHLOROPHENOL

CAS No. 87-86-5

C_6HOCl_5 Molecular weight 266.3

Synonyms or common names: chlorophen; PCP; penchlorol; penta; pentachlorofenol; pentachlorofenolo; pentachlorphenol; 2,3,4,5,6-pentachlorophenol

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

Physical and Chemical Properties, Production, and Use

Pure pentachlorophenol exists as white to light tan needlelike crystals at room temperature (Table 1). It is also available as potassium pentachlorophenate. Pentachlorophenol has a pungent odor when heated (Merck, 1976), and sodium pentachlorophenate has a sharp odor at room temperature because of partial hydrolysis (Crosby et al., 1981). Technical-grade pentachlorophenol occurs as brown flakes, and technical-grade sodium pentachlorophenate consists of cream-colored beads. Pure pentachlorophenol is nonflammable and noncorrosive, but it causes corrosion of rubber in oil solution (Mercier, 1981). Pentachlorophenol is produced by two methods: direct chlorination of phenols or hydrolysis of hexachlorobenzene. The former method is the one used in the United States (Crosby et al., 1981).

Technical-grade pentachlorophenol contains a large number of impurities. The most important of these are other chlorophenols, particularly isomers of tetrachlorophenol, and several important microimpurities such as polychlorinated dibenzodioxins (CDDs) and polychlorinated dibenzofurans (CDFs). The manufacturing method, date of manufacture, and degree of postmanufacture "clean-up" determine which impurities are present and the level of contamination (Crosby

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF PENTACHLOROPHENOL (a)

Melting point: 191° C
Boiling point: 310° C at 760 mm mercury
Specific gravity: 1.98
Vapor pressure: 0.12 mm mercury at 100° C
Relatively insoluble in water (0.0014 g/100 g at 20° C) unless it is in a salt form, such as sodium pentachlorophenate, which is readily soluble (greater than 200 g/100 g at 20° C)
Relatively soluble in common solvents at 25° C; e.g., acetone: 50 g/100 g; benzene: 15 g/100 g; ethanol (95%): 120 g/100 g; methanol: 180 g/100 g

(a) IPCS, 1987

et al., 1981). CDDs and CDFs also may be formed when materials containing pentachlorophenol are burned, especially at temperatures below 500° C (Jansson et al., 1978; Buser, 1982).

Although precise estimates are not possible, global production of pentachlorophenol together with its salts was estimated to be 90,000 metric tons (MTs) (IRPTC, 1983). Increasing restrictions (Fed. Regist., 1984, 1988) in the last few years and alternative methods of wood preservation have probably reduced this amount. Current world production is approximately 17 MTs, with the United States accounting for 12.7 MTs of this amount (Vulcan Chemical, personal communication). In Sweden, all uses of pentachlorophenol were banned in 1977 (Ahlborg and Thunberg, 1980).

Pentachlorophenol has a wide range of uses, primarily because pentachlorophenol and its salts are powerful wide-spectrum biocides, are relatively persistent in the environment, and are relatively inexpensive. Therefore, they have been used in industry and agriculture and domestically as algicides, bactericides, fungicides, herbicides, insecticides, and molluscicides. Currently in the United States, about 80% of pentachlorophenol is used for wood treatment, 6% for slime control, and the rest for miscellaneous purposes (Crosby et al., 1981). Use patterns are comparable in other countries (Jones, 1981; Angerer, 1984). For the treatment of wood, pentachlorophenol is usually used as a 5% solution in No. 2 fuel oil or kerosene (Cirelli, 1978) or in methylene chloride, isopropyl alcohol, or methanol (Ingram et al., 1981). Concentrations between 4,000 and 6,000 ppm have been detected on the surface of wood treated with pentachlorophenol (Gebefuegi et al., 1979).

The major source of human exposure relates to pentachlorophenol's ubiquitous use and its volatility and to the high water solubility of its commonly used salts. In urban areas, pentachlorophenol has been found in air at concentrations of 5.7-7.8 ng/m^3. Even in remote mountain air, it has been found at a concentration of 0.25-0.93 ng/m^3. It has also been found in rain or snow in North America and Europe (Jones, 1981; Rosskamp, 1982). Most occupational exposure to pentachlorophenol is related to its use as a wood preservative and occurs via inhalation or dermal contact. This includes exposure of workers during wood treatment and, subsequently, of the general population by stream and well water contamination (Thompson et al., 1978). Most workplace concentrations are below the time-weighted-average/maximum-allowable-concentration value of 500 µg/m^3 (ACGIH, 1980). High exposure has been reported for agricultural workers, expecially those involved in spraying applications (Demidenko, 1969). Although pentachlorophenol is contraindicated for indoor use, significant inhalation exposure has occurred in closed spaces where treated wood was used on interior surfaces (Krause, 1982; Saur et al., 1982). As much as 80% of the pentachlorophenol may evaporate from treated wood within 12 months if brushed on the surface (Petrowitz, 1981). Pressure treatment and use of different solvents will slow this process (Ingram et al., 1981).

Pentachlorophenol can be leached from the soil at a rate that depends on soil type and pH (absorption decreases with rising pH) and the amount of water percolating through the soil (Haque and Freed, 1974). Interestingly, the CDD and CDF impurities are not volatile and do not readily leach from soil (Young et al., 1978). Pentachlorophenol can be degraded by light or by micro-organisms in soil and water (Cserjesi, 1972; Watanabe, 1973; Wong and Crosby, 1981; Trevors, 1982). Several pathways for biodegradation in soil have been suggested: methylation to pentachlorophenol methyl ether or pentachloroanisole, acylation of the hydroxyl group, dechlorination to tetrachlorophenol, or hydroxylation to tetrachlorodihydroxybenzenes (Rott et al., 1979). Conditions of low oxygen concentration are generally unfavorable for biodegradation, and significant amounts of pentachlorophenol can be found in underwater sediments, which generally contain more pentachlorophenol than the overlying water (Boyle et al., 1980). Heavy contamination of soil and water can be found near industrial discharges, and pentachlorophenol has been found in well water at concentrations as high as 50 µg/liter (Wong and Crosby, 1981).

Other means of human exposure include pentachlorophenol-treated leather, textiles, paper

products, and food packaging (Fed. Regist., 1977; Heikes and Griffitt, 1980). Bioaccumulation in the marine food chain has been documented, and fish kills have resulted. Agricultural use of pentachlorophenol has resulted in contamination of wild birds. Chickens have had to be discarded because of a musty taint to the flesh after they were raised on bedding containing pentachloroanisole, a metabolite of pentachlorophenol biodecomposition (Curtis et al., 1972). The total dietary intake of pentachlorophenol for the period 1965-70 in the United States was calculated to range from 1 to 6 µg per person per day (Duggan and Corneliussen, 1972), with higher estimated total exposure if the person is exposed to treated wood (Fischer, 1983). Pentachlorophenol at the microgram per liter level has been found in the urine of people not occupationally exposed (Klemmer et al., 1980).

Metabolism

Pentachlorophenol is readily absorbed following the inhalation, dermal, and ingestion routes of exposure (IPCS, 1987) and is distributed to all tissues of the body; the levels in liver and kidney are particularly high, whereas those in fat, brain, and muscle are relatively low (Larsen et al., 1972; Braun et al., 1977). In rodents, metabolism occurs via oxidation to tetrachlorohydroquinone and to a lesser extent to trichlorohydroquinone, as well as by glucuronidation (Jakobson and Yllner, 1971; Ahlborg and Thunberg, 1980). In humans and monkeys, metabolism to tetrachlorohydroquinone has not been observed. In male volunteers, pentachlorophenol was eliminated as both the parent compound and the glucuronide; no other metabolites were observed (Braun and Sauerhoff, 1976; Braun et al., 1979; Uhl et al., 1986). Pentachlorophenol and/or these metabolites are excreted mainly in urine in rodents (62%-83%) and monkeys (45%-75%). In fact, urinary metabolites are used as indicators of pentachlorophenol exposure (IPCS, 1987).

The biologic half-life of pentachlorophenol is relatively short, and bioaccumulation is only slight. After a single exposure of rats or mice, the initial half-life was 6-27 hours, but a second and slower elimination phase had a half-life of 33-374 hours (Larsen et al., 1972; Braun et al., 1977). The proposed explanation for the biphasic elimination was that a portion of pentachlorophenol and/or its metabolites escapes initial elimination and becomes involved in an enterohepatic circulation or may be bound to plasma proteins (Braun and Sauerhoff, 1976). The half-life in monkeys is longer (41-92 hours) than the initial elimination phase in rodents.

The elimination kinetics in humans are less clear. After a single oral exposure of 0.1 mg sodium pentachlorophenate/kg body weight, a half-life of 30 hours (plasma) was observed, with elimination primarily of the parent compound in urine (Braun et al., 1979). Over 90% was eliminated from the body within 7 days. However, the half-life depends to a great degree on the dose, vehicle, and salt used. A dose of 0.016 mg/kg in 40% ethanol resulted in a substantially longer half-life in plasma of 16 days (presumably because of more complete protein binding) (Uhl et al., 1986). Small amounts of pentachlorophenol may be stored for long periods in the body.

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

Animal Toxicity

Pentachlorophenol has widespread toxic effects on many parts of the ecosystem, on both unicellular and multicellular organisms, and on plants as well as on animals. Also, biomagnification occurs in the food chain, particularly in marine environments (IPCS, 1987).

The effectiveness of pentachlorophenol as a microbicide is well known and is one of the specific uses of the chemical. It has also been used as a molluscicide in aquatic environments but has the potential to be toxic to the beneficial (desired) members of this class (Adema and Vink, 1981). There are marked differences in species sensitivity, but both terrestrial and aquatic plants are susceptible to the toxic effects of pentachlorophenol (USEPA, 1979; Buikema et al., 1979). For example, although only 0.19 mg/liter

is required to kill duckweed (*Lemna minor*) (Blackman et al., 1955), 80 mg/liter is required to kill water hyacinth (*Crassipes eichornia*) (Hirsch, 1942). In general, many invertebrates are susceptible to the toxic effects of pentachlorophenol; embryos, larvae, and nymphs are more affected (on a milligram per kilogram basis) than are adults. The 96-hour LC_{50} value for pentachlorophenol for the young marine decapod *Palaemon elegans* is 130 times lower than that for the adult of the same species (Dijk et al., 1977). Very few long-term studies of pentachlorophenol have been conducted in animals or plants. Most of the short-term studies have stressed the lethal effects of pentachlorophenol; very little is known about the sublethal effects in either plants or animals (IPCS, 1987).

Many studies have been conducted on the effects of pentachlorophenol in fish, but few have compared pure pentachlorophenol with various commercial preparations. Immature fish are more susceptible than are the adults to the toxic effects of pentachlorophenol. Pentachlorophenol is toxic to most fish species at the microgram per liter level, and the degree of toxicity may be related to the impurities found in commercial preparations. For example, in 90-day studies fathead minnows (*Pimephases promelas*) were more resistant to pure pentachlorophenol and Dowicide EC-7 than to a less pure commercial grade contaminated with relatively large quantities of hexachlorobenzene, chlorophenoxyphenols, CDDs, and CDFs (Cleveland et al., 1982).

The majority of toxicity data on pentachlorophenol in domestic animals comes from laboratory studies, although a few accidental exposures have occurred. Most "spontaneous" toxicity resulted from the animals' being housed in structures built with recently treated wood that "bled." Animals, particularly pigs, appear to preferentially lick such wood, possibly because of its salty taste (Blevins, 1965; Ryan, 1983). In a 160-day study of cattle exposed continuously to feed containing pure or technical-grade pentachlorophenol at fairly high levels (15-20 mg/kg per day), very little toxicity was observed except in the technical-grade pentachlorophenol group (McConnell et al., 1980). The authors concluded that impurities were the major cause of toxicity in this study (Parker et al., 1980).

In laboratory rodents, pentachlorophenol is moderately toxic. The acute oral LD_{50} value in rats ranges from 27 to 205 mg/kg (IPCS, 1987). Signs of acute toxicity in rodents include hyperthermia, muscle tremors and spasms, and loss of righting reflex. Death is usually due to respiratory paralysis. Pentachlorophenol is toxic by all routes of exposure, but more is required for a given effect by the dermal route than by the oral, intravenous, or inhalation routes. In rats, pentachlorophenol has been reported to be at least 10 times more toxic after inhalation exposure than after oral exposure (Hoben et al., 1976).

Target organs of pentachlorophenol toxicity are primarily the liver, kidney, and bone marrow. The liver of most exposed mammals is usually enlarged but may show little other overt toxicity in short-term studies. The hepatic enlargement was explained as being due to proliferation of the endoplasmic reticulum (McConnell, 1980). Other lesions reported in the liver include hepatocellular pleomorphism, necrosis, degeneration, and biliary hyperplasia (IPCS, 1987).

Subcellular distribution studies of pentachlorophenol show it to be six times more concentrated in the microsomal fraction than in the mitochondria and two times more than in the cytosol (Arrhenius et al., 1977a,b). Pentachlorophenol also stimulates the production of the hepatic enzymes aryl hydrocarbon hydroxylase (AHH) and glucuronyl transferase and of cytochrome P450, but most of the increase in these enzymes may be due to the presence of CDDs and CDFs, which are known to be powerful inducers of these liver enzymes (Goldstein et al., 1977; Kimbrough and Linder, 1978). Porphyrin production and urinary excretion also are increased in rodents exposed to technical-grade pentachlorophenol, but again the primary cause may be the impurities (Wainstock de Calmanovici and San Martin de Viale, 1980).

Laboratory studies of technical-grade pentachlorophenol routinely show slight decreases in hemoglobin levels and a reduction in the number of circulating erythrocytes (Johnson et al.,

1973; Knudsen et al., 1974). Immunologic studies of technical-grade pentachlorophenol in cattle suggest a specific effect of impurities on bone marrow, which is reflected in alterations in cell-mediated immunity (McConnell et al., 1980). Pure pentachlorophenol did not appear to be immunotoxic. Similar immunologic results have been observed in mice (Kerkvliet et al., 1982a,b). Kerkvliet and coworkers found reduced humoral immunity as well as effects on cellular immunity with technical-grade pentachlorophenol but not with analytical-grade pentachlorophenol. In contrast, studies in rats conducted with pure pentachlorophenol showed enhanced cellular immunity (Exon and Koller, 1983a).

Lesions in the urinary tract have been observed both in laboratory studies and spontaneous poisonings and are more readily observed after long-term exposure. The basic lesion is urothelial proliferation, which subsequently shows inflammatory changes (cystitis and nephritis) of varying severity (Kinzell et al., 1981). Again, the severity of the lesions is directly related to the level of the impurities (McConnell, 1980).

Reproductive and Developmental Toxicity

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

Technical-grade pentachlorophenol when given to rats at 5 mg/kg per day between gestation days 6 and 15 did not cause any effects in the fetus or dam (Schwetz et al., 1974). Fetal resorptions and delayed development were observed at 15 mg/kg per day, and maternal toxicity occurred at 35 mg/kg (Cirelli, 1978). More limited fetotoxicity was observed in a similar study in rats (Courtney et al., 1976). In another study, pentachlorophenol appeared to be more embryotoxic than the metabolite pentachloroanisole (Welsh et al., 1987). According to one report, very high maternal exposure of rats at 60 mg/kg per day resulted in dwarfism, exencephaly, macrophthalmia, and absence of a tail in some fetuses (Edwards, 1968). However, these effects were attributed to hyperthermia in the dam, a well-known consequence of pentachlorophenol toxicity. Interestingly, technical-grade pentachlorophenol appears to be less fetotoxic than the pure grade. The explanation for this appears to be the presence of CDDs and CDFs that stimulate the liver enzymes necessary for pentachlorophenol metabolism (NRCC, 1982). However, some of these impurities are well-known teratogens (Courtney and Moore, 1971). It is probable that teratogenic effects have not been observed because exposure to the impurities is well below the teratogenic dose.

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

Carcinogenicity

Most of the long-term studies of pentachlorophenol, especially those designed to evaluate carcinogenesis in mice, are confounded by various design flaws such as the presence of known carcinogenic impurities, short exposure/observation time, or use of a dose well below the maximum tolerated dose. The only long-term study of pentachlorophenol in mice did not show any neoplastic effect in two hybrid strains (Innes et al., 1969). However, the study was terminated at 18 months, which may have not been long enough to detect carcinogenic effects. The only in-depth study of pure pentachlorophenol of adequate duration (2 years) in rats did not show evidence of carcinogenicity (Schwetz et al., 1978). However, the lack of body weight or organ weight changes at the highest dose (30 mg/kg) suggests that the rats might have tolerated a higher dose, and the number of rats per dose group (25) was small. Studies in female rats with ethylnitrosourea (prenatal exposure) and pentachlorophenol (postnatal exposure) did not show any clearly discernible cocarcinogenic effects (Exon and Koller, 1983b). In long-term studies in rodents, a mixture of hexachlorodibenzo-*p*-dioxins (HxCDDs) (some of the dioxin impurities found in technical-grade pentachlorophenol) were carcinogenic, causing neoplasms of the thyroid gland and liver (NCI, 1980). Although not found

in pentachlorophenol, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has also been shown to be carcinogenic in rodents (NTP, 1982) and is the most potent carcinogenic promoter ever studied (Pitot et al., 1980).

Genetic Toxicity

Pentachlorophenol does not appear, on the basis of the NTP test results and data presented in the literature, to be a strong gene mutagen, but there is some indication that it has clastogenic potential. Results of all bacterial tests for induction of gene mutation (Anderson et al., 1972; Shirasu, 1975; Simmon and Kauhanen, 1978; Haworth et al., 1983; Table 32; Moriya et al., 1983) or growth inhibition due to DNA damage (Shirasu, 1975) by pentachlorophenol are negative with the exception of a study by Nishimura et al. (1982) using phenobarbital- or 5,6-benzoflavone-induced rat liver S9.

Results of tests for induction of gene mutation in *Saccharomyces cerevisiae* by pentachlorophenol were positive (Fahrig, 1974; Fahrig et al., 1978), but the chemical did not produce mitotic recombination (Simmon and Kauhanen, 1978). Pentachlorophenol did not induce chromosome nondisjunction or sex chromosome loss in Drosophila (Ramel and Magnusson, 1979). Results of tests for chromosomal or meiotic effects in plant cells (flowers and roots of *Vicia faba* or *Allium cepa*) were positive (Amer and Ali, 1968, 1969; Sikka and Sharma, 1976). Sodium pentachlorophenate did not induce sex-linked recessive lethal mutations when fed to adult male Drosophila for 3 days as a 7.0 µM solution in sucrose (Vogel and Chandler, 1974).

Casto (1981) reported dose-related increases in the SA7 viral transformation frequency of Syrian hamster embryo cells treated with 50 or 100 µg/ml pentachlorophenol. In NTP cytogenetic assays with cultured Chinese hamster ovary cells, treatment with pentachlorophenol (91.6% pure) produced an increase in the frequency of sister chromatid exchanges (SCEs) in the absence, but not in the presence, of rat liver S9 (Galloway et al., 1987; Table 33). In contrast, chromosomal aberrations were induced in these cells by pentachlorophenol but only in the presence of S9 (Table 34). Overall, pentachlorophenol was concluded to be weakly positive in these cytogenetic assays (Galloway et al., 1987).

Major impurities identified in the pentachlorophenol material used for NTP genetic toxicology studies were tetrachlorophenol (6.5%) and octachlorodibenzo-*p*-dioxin (OCDD) (2%). OCDD and all three tetrachlorophenols, the 2,3,4,5-, 2,3,4,6-, and 2,3,5,6- isomers, were negative when tested in Salmonella by the NTP preincubation protocol (Zeiger et al., 1988). Cytogenetic tests have been completed only on 2,3,5,6-tetrachlorophenol, and results were positive for both SCE and chromosomal aberrations. This isomer was positive for SCEs both with and without S9 and positive for aberrations only in the presence of S9, just as was the pentachlorophenol containing these impurities.

Another major contaminant was hexachlorobenzene (10 ppm). Although NTP Salmonella mutagenicity tests were negative (Haworth et al., 1983) for this compound, mutation induction by hexachlorobenzene was reported by two other laboratories. The first study reported gene reversion in *S. cerevisiae* 632/4 after treatment with 100 ppm hexachlorobenzene (Guerzoni et al., 1976), and the second study reported "detectable mutagenesis" at a rate of 7.5×10^{-5} mutations per locus in the nematode *Panagrellus redivivus* (Samoiloff et al., 1980). Results of tests for induction of dominant lethal mutations in rodents were negative (Khera, 1974; Simon et al., 1979).

Pentachlorophenol has been tested for genetic toxicity in vivo in only two mammalian tests. It was positive in a mammalian spot test in which (C57BL/6JHan × T-stock)F_1 mice were administered the chemical (99% pure) at 0-100 mg/kg (Fahrig et al., 1978). Male (C57BL/6 × C3H)F_1 mice dosed at up to 400 mg/kg per day with "reagent-grade" (purity not stated) pentachlorophenol for 5 days did not exhibit abnormal sperm morphology or decreases in testicular weight or epididymal sperm counts (Osterloh et al., 1983).

Study Rationale

Pentachlorophenol was selected for study because of high production, widespread population exposure, and lack of carcinogenicity and specialized toxicology data. Feed was selected as the route of administration because absorption is adequate by this route and this route is one

with known human exposure. Four grades of pentachlorophenol (pure, EC-7, DP-2, or technical grade) containing varying levels of impurities were evaluated in 30-day or 6-month studies. The technical grade of pentachlorophenol was the primary focus of these and the 2-year studies because it has been the principal material used commercially and therefore the substance to which people most often have been exposed. Dowicide EC-7 was also selected for 2-year studies because it contains smaller quantities of toxic impurities that have been speculated to be a major cause of the chronic toxicity of pentachlorophenol. The studies were conducted only in $B6C3F_1$ mice because results of a previous study in Sprague Dawley rats (Schwetz et al., 1978) were considered adequate and negative at that time. Economic considerations (cost of an additional species vs. an additional type of pentachlorophenol and supplemental studies) also played an important role in this decision.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROPHENOL
- Technical-Grade Pentachlorophenol
- Pentachlorophenol, Dowicide EC-7
- Pentachlorophenol, DP-2
- Pure Pentachlorophenol
- Stability and Storage

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

THIRTY-DAY STUDIES

SIX-MONTH STUDIES

TWO-YEAR STUDIES
- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

GENETIC TOXICOLOGY

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PENTACHLOROPHENOL

Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). Reports on analyses performed in support of the pentachlorophenol studies are on file at NIEHS.

Technical-Grade Pentachlorophenol

A composite lot (lot no. MB-528) of technical-grade pentachlorophenol was obtained in one lot from the AWPI Subcommittee on Pentachlorophenol (Table 2). The chemical was labeled as an industry composite prepared from material supplied by Monsanto Industrial Chemical Co., Reichhold Chemicals, Inc., and Vulcan Materials Co. Lot no. MB-528 was obtained as pale brown microcrystals with a melting point of 154.0°-181.5° C. The identity of technical-grade pentachlorophenol was confirmed by spectroscopic analysis. The infrared spectrum (Figure 1) was consistent with the literature spectrum (Sadtler Standard Spectra) except that peaks at 1,450 and 2,900 cm^{-1} were missing. The ultraviolet/visible and nuclear magnetic resonance (Figure 2) spectra were consistent with those expected for the structure.

The purity of lot no. MB-528 was determined by elemental analysis, Karl Fischer water analysis, titration of the phenol group with sodium hydroxide, and gas chromatography with flame ionization detection, a nitrogen carrier at a flow rate of 40-70 ml/minute, and a 1% SP1240 DA column (system 1) or a 10% SP2100 column (system 2). Cumulative data indicated that lot no. MB-528 was 90.4% pure. Results of elemental analyses agreed with theoretical values for hydrogen and were slightly high for carbon and slightly low for chlorine. Water content was 0.09%. Titration of the phenol group indicated a purity of 96.3%. Gas chromatography by system 1 indicated one impurity with an area 6.2% of the major peak area. Gas chromatography by system 2 indicated four impurities. One of the impurities had an area of 2.6%, and a second (an unresolved shoulder of the major peak) had an area estimated to be 0.7%-3.5% of the major peak area. The other two impurities had a combined relative area of 0.28%. This lot of technical-grade material was found by gas chromatographic system 1 to contain 90.4% pentachlorophenol (corrected for 98.6% purity of the standard) when compared with a reference sample of pentachlorophenol (pure pentachlorophenol, Aldrich Chemical Co., lot no. AC102777). Impurities in the technical-grade study material were

TABLE 2. IDENTITY AND SOURCE OF PENTACHLOROPHENOL USED IN THE FEED STUDIES

Thirty-Day Studies	Six-Month Studies	Two-Year Studies
Lot Numbers		
Pure pentachlorophenol--AC102777; technical-grade pentachlorophenol--MB-528; pentachlorophenol, Dowicide EC-7--05217D	Pentachlorophenol, DP-2--MM11199; other formulations same as 30-d studies	Technical-grade pentachlorophenol and Dowicide EC-7--same as 30-d studies
Date of Initial Use		
6/15/79	6/2/80	4/14/82
Supplier		
Pure pentachlorophenol--Aldrich Chemical Co. (Milwaukee, WI); technical-grade pentachlorophenol--AWPI Subcommittee on Pentachlorophenol (composite of technical-grade materials produced by Monsanto Industrial Chemical Co., St. Louis, MO, Reichhold Chemicals, Inc., White Plains, NY, and Vulcan Materials Co., Birmingham, AL); pentachlorophenol, Dowicide EC-7--Dow Chemical U.S.A. (Midland, MI)	Pentachlorophenol, DP-2--Dow Chemical U.S.A. (Midland, MI); other formulations--same as 30-d studies	Technical-grade pentachlorophenol and pentachlorophenol, Dowicide EC-7--same as 30-d studies

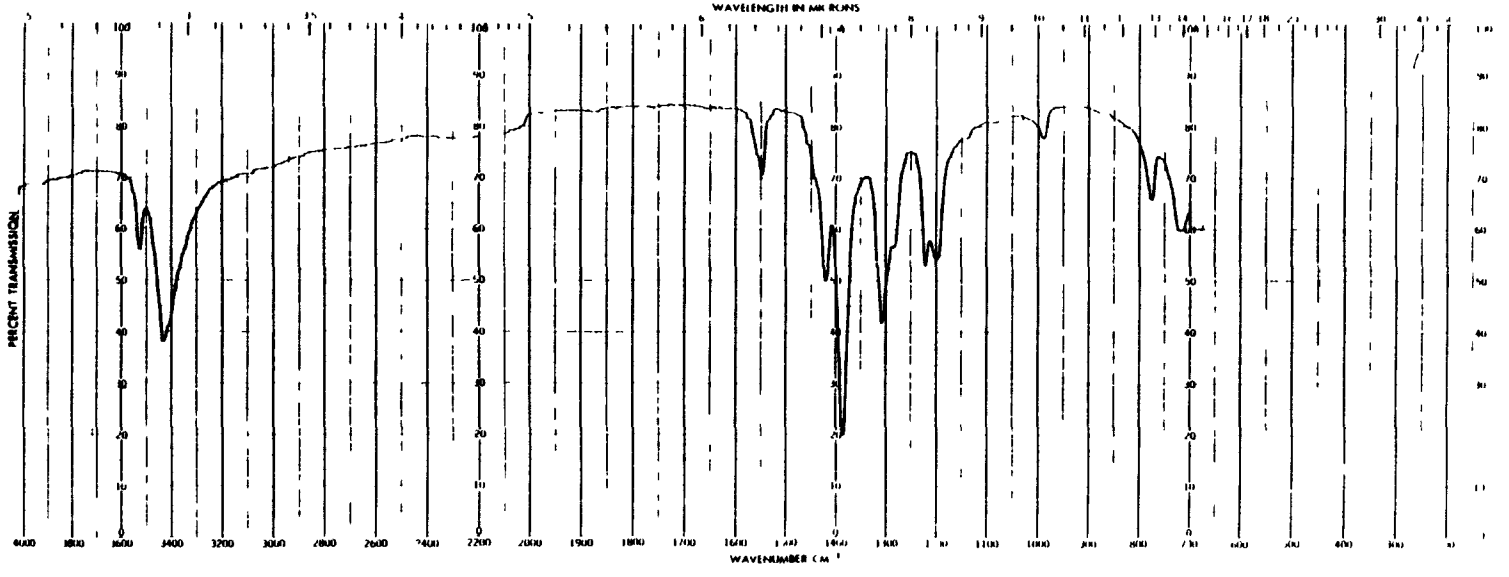


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF TECHNICAL-GRADE PENTACHLOROPHENOL (LOT NO. MB-528)

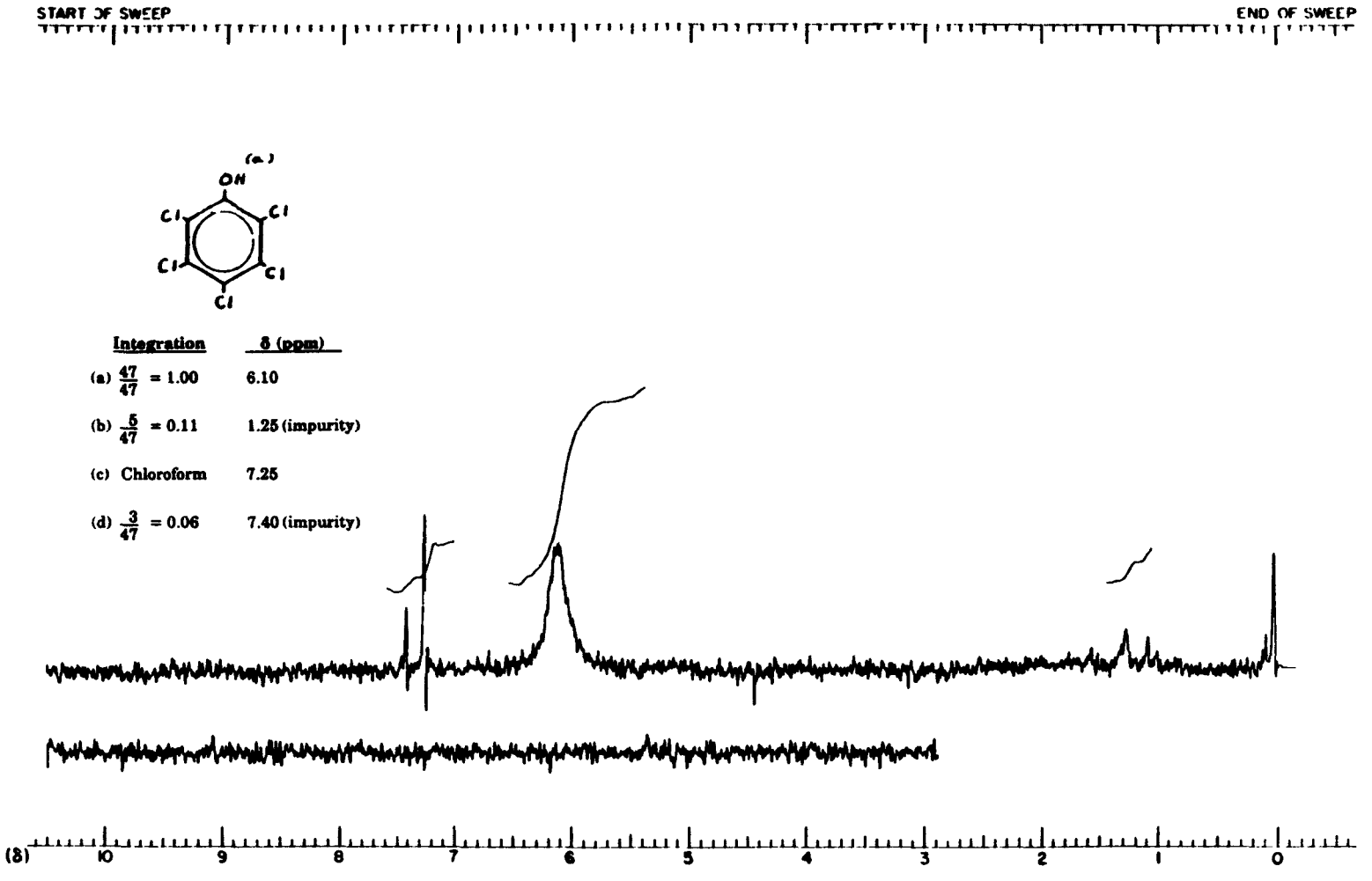


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TECHNICAL-GRADE PENTACHLOROPHENOL (LOT NO. MB-528)

identified and quantitated by gas chromatography/mass spectrometry (Table 3).

Pentachlorophenol, Dowicide EC-7

Pentachlorophenol, Dowicide EC-7 (hereafter referred to in text as Dowicide EC-7 or EC-7), was obtained in one lot (lot no. 05217D) from Dow Chemical U.S.A. (see Table 2). Lot no. 05217D was obtained as cream-colored microcrystals with a melting point of 161.0°-181.5° C. The infrared spectrum was consistent with the literature spectrum (Sadtler Standard Spectra) except that the peak at 2,900 cm^{-1} was missing (Figure 3). The ultraviolet/visible and nuclear magnetic resonance (Figure 4) spectra were consistent with those expected for the structure.

The purity of Dowicide EC-7 was determined by the same methods used for the technical-grade material. Cumulative data indicated that the Dowicide EC-7 study material was approximately 91% pure. Results of elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values. Water content was 0.07%. Titration of the phenol group indicated a purity of 101.2%. Gas chromatographic system 1 indicated seven impurities, one with an area 12% of the major peak area and the remaining six impurities with a combined relative area of 1.9%. Gas chromatographic system 2 indicated two impurities with relative areas of 9.7% and 0.03%. The Dowicide EC-7 study material was found by gas chromatographic analysis to contain 91.0% pentachlorophenol when quantitated against a sample of pentachlorophenol that was 98.6% pure (pure pentachlorophenol, Aldrich Chemical Co., lot no. AC102777). Impurities in Dowicide EC-7 were identified and quantitated (see Table 3).

TABLE 3. RESULTS OF ANALYSES FOR IMPURITIES IN THE PENTACHLOROPHENOL USED IN THE THIRTY-DAY, SIX-MONTH, AND TWO-YEAR FEED STUDIES (a)

Impurity	Pure	Technical Grade	DP-2	Dowicide EC-7 (b)
Dichlorophenol	--	--	(c) 0.013%	--
Trichlorophenol	<0.01%	0.01%	(d) 0.044%	(e) 0.007%
Tetrachlorophenol	1.4%	3.8%	(f) 7.0%	9.4%
Hexachlorobenzene	10 ppm	50 ppm	15 ppm	65 ppm
Tetrachlorodibenzodioxin	<0.08 ppm	--	--	<0.04 ppm
Hexachlorodibenzodioxin	<1 ppm	10.1 ppm	0.59 ppm	0.19 ppm
Heptachlorodibenzodioxin	--	296 ppm	28 ppm	0.53 ppm
Octachlorodibenzodioxin	<1 ppm	1,386 ppm	173 ppm	0.69 ppm
Pentachlorodibenzofuran	--	1.4 ppm	--	--
Hexachlorodibenzofuran	--	9.9 ppm	12.95 ppm	0.13 ppm
Heptachlorodibenzofuran	--	88 ppm	172 ppm	0.15 ppm
Octachlorodibenzofuran	--	43 ppm	320 ppm	--
Heptachlorohydroxydiphenyl ether	0.01%	(g) 0.11%	(g) 0.05%	--
Octachlorohydroxydiphenyl ether	0.09%	1.91%	1.41%	--
Nonachlorohydroxydiphenyl ether	0.21%	3.56%	2.21%	--
Hexachlorohydroxydibenzofuran	0.11%	0.16%	0.07%	--
Heptachlorohydroxydibenzofuran	0.22%	0.47%	0.31%	--
Not quantitated	--	--	(h)	--

(a) Samples were dissolved in benzene, placed on a deactivated alumina column, and eluted with benzene. Further separation was carried out with a basic aluminum oxide column; elution was with methylene chloride in hexane. Identification was performed by gas chromatography with an SP2100 capillary column/mass spectrometry; quantitation was by comparison with spiked samples analyzed by gas chromatography with an SP1240 DA column.
(b) Four unidentified impurities with concentrations of 0.14, 0.057, 0.045, and 0.035 ppm were also detected.
(c) Probably the 2,4-isomer
(d) Probably the 2,4,6-isomer
(e) Identified as the 2,3,6-isomer; another isomer was believed to be present but was not identified.
(f) Probably the 2,3,4,6-isomer
(g) Includes octachlorodiphenyl ether
(h) Two isomers each of hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl were identified.

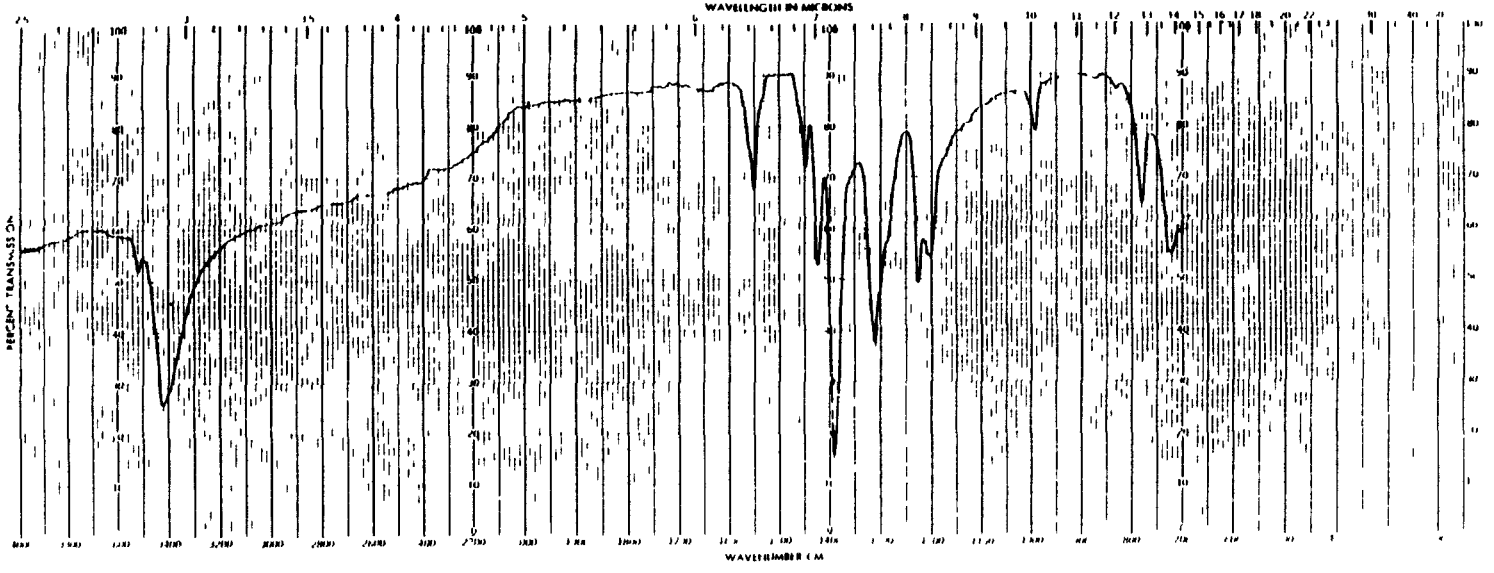


FIGURE 3. INFRARED ABSORPTION SPECTRUM OF PENTACHLOROPHENOL, DOWICIDE EC-7 (LOT NO. 05217D)

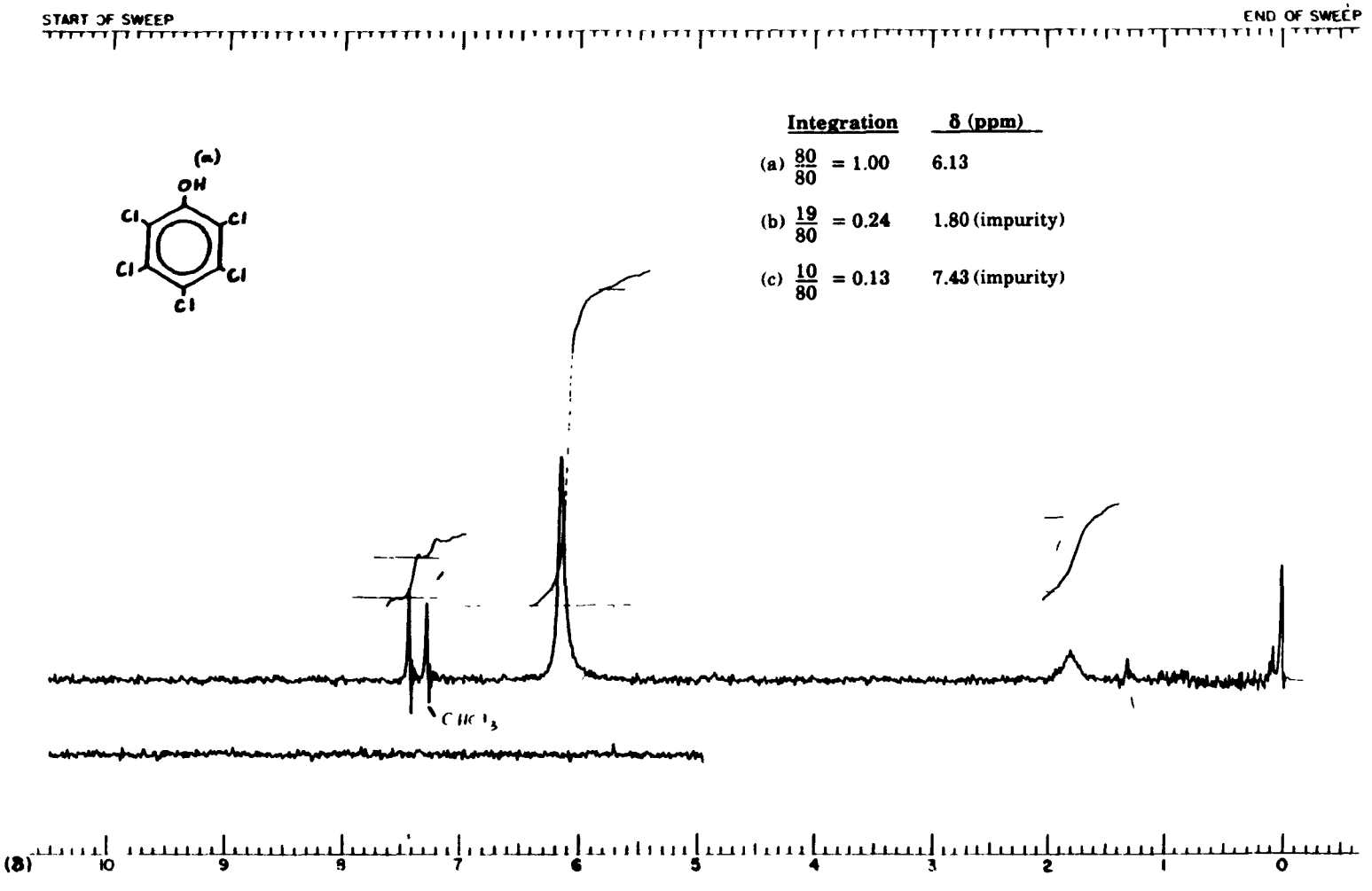


FIGURE 4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PENTACHLOROPHENOL, DOWICIDE EC-7 (LOT NO. 05217D)

Pentachlorophenol, DP-2

Pentachlorophenol, DP-2 (hereafter referred to in the text as DP-2), was obtained in one lot (lot no. MM11199) from Dow Chemical U.S.A. (see Table 2). Lot no. MM11199 was obtained as a light brown microcrystalline powder with a melting point of 163°-181° C. The infrared spectrum was consistent with the literature spectrum (Sadtler Standard Spectra) except that the peak at 2,900 cm^{-1} was missing (Figure 5). The ultraviolet/visible and nuclear magnetic resonance (Figure 6) spectra were consistent with those expected for the structure.

The purity of DP-2 was determined by the same methods used for the technical-grade material. Cumulative data indicated that the DP-2 study material was approximately 91.6% pure. Results of elemental analyses agreed with the theoretical values. Water content was 0.027%. Titration of the phenol group gave a purity of 99.2%. Gas chromatographic system 1 indicated five impurities, one with an area 11% of the major peak area and the remaining four impurities with a combined relative area of 0.08%. Gas chromatographic system 2 indicated at least six impurities, one with an area 9.8% of the major peak area and five impurities with a combined relative area of 2.1%, two of which may have been multiple, unresolved peaks. The DP-2 study material was found by gas chromatographic analysis to contain 91.6% pentachlorophenol when quantitated against a sample of pentachlorophenol which was 98.6% pure (pure pentachlorophenol, Aldrich Chemical Co., lot no. AC102777). Impurities were identified and quantitated (see Table 3).

Pure Pentachlorophenol

Pure pentachlorophenol was obtained in one lot (lot no. AC102777) from Aldrich Chemical Co. (see Table 2). Lot no. AC102777 was obtained as cream-colored microcrystals with a melting point of 186.5°-189.0° C (literature value, 190°-191° C; Merck, 1976). The infrared spectrum was consistent with the literature spectrum (Sadtler Standard Spectra) except that peaks at 1,450 and 2,900 cm^{-1} were missing (Figure 7). The ultraviolet/visible and nuclear magnetic resonance (Figure 8) spectra were consistent with those expected for the structure.

The purity of lot no. AC102777 was determined by the same methods used for the technical-grade material. Cumulative data indicated a purity of 98.6%. Results of elemental analyses agreed with the theoretical values. Water content was 0.15%. Titration of the phenol group indicated a purity of 100.5%. Gas chromatographic system 1 indicated two impurities. One impurity had an area 1.8% of the major peak area, and the other impurity had a relative area of 0.08%. Analysis with system 2 gave broad peaks that were difficult to quantitate and was considered to be less accurate than analysis performed with system 1. Impurities in the pure pentachlorophenol study material were identified and quantitated (see Table 3).

Stability and Storage

Stability studies of the bulk chemical were conducted with the pure pentachlorophenol study material (lot no. AC102777). Purity analysis by gas chromatography with a 1% SP1240 DA column, a nitrogen carrier, and flame ionization detection indicated that pure pentachlorophenol was stable when stored at temperatures up to 60° C for 2 weeks. Technical-grade pentachlorophenol and Dowicide EC-7 were stored at room temperature during the 30-day and 6-month studies and at 4° C during the 2-year studies. Pure pentachlorophenol and DP-2 were stored at room temperature throughout the 6-month studies. Confirmation of the stability of the bulk chemicals during the toxicity studies was obtained by the gas chromatographic system previously described. No degradation was seen over the course of the studies. Chemical identity was confirmed at the study laboratory by infrared spectroscopy.

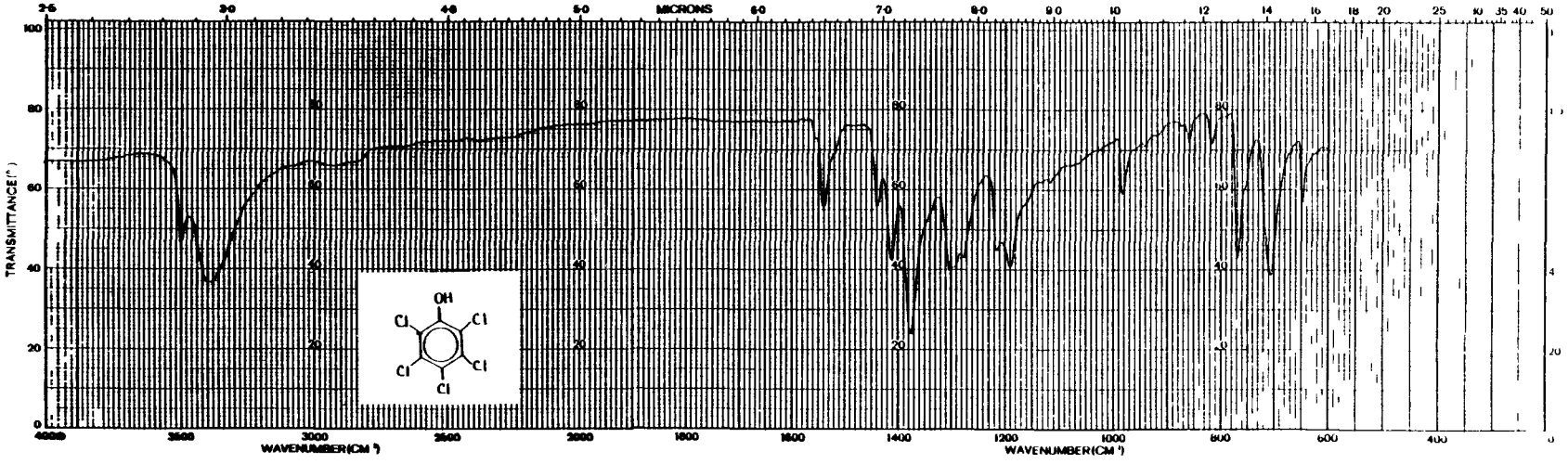


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF PENTACHLOROPHENOL, DP-2 (LOT NO. MM11199)

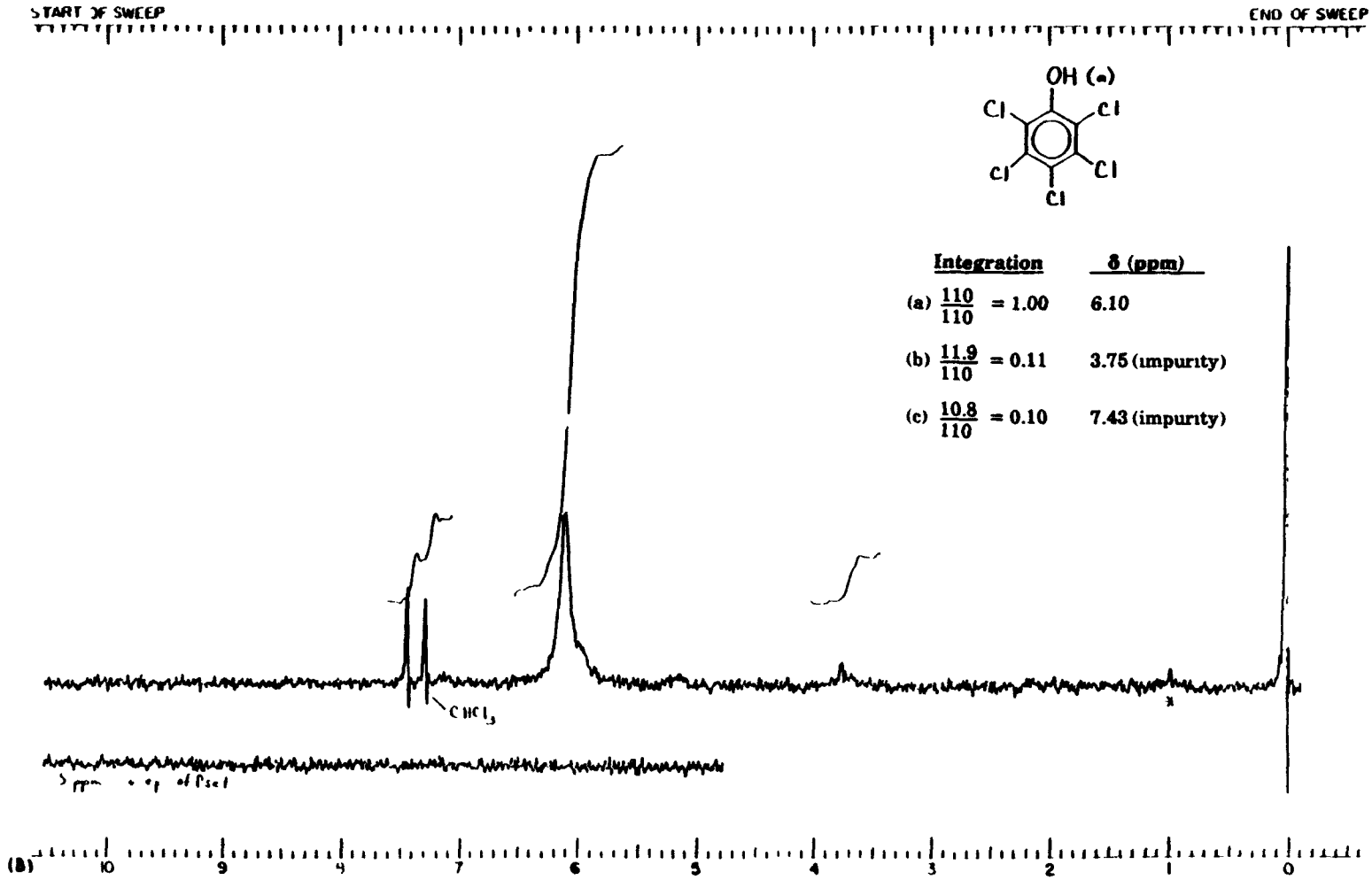


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PENTACHLOROPHENOL, DP-2 (LOT NO. MM11199)

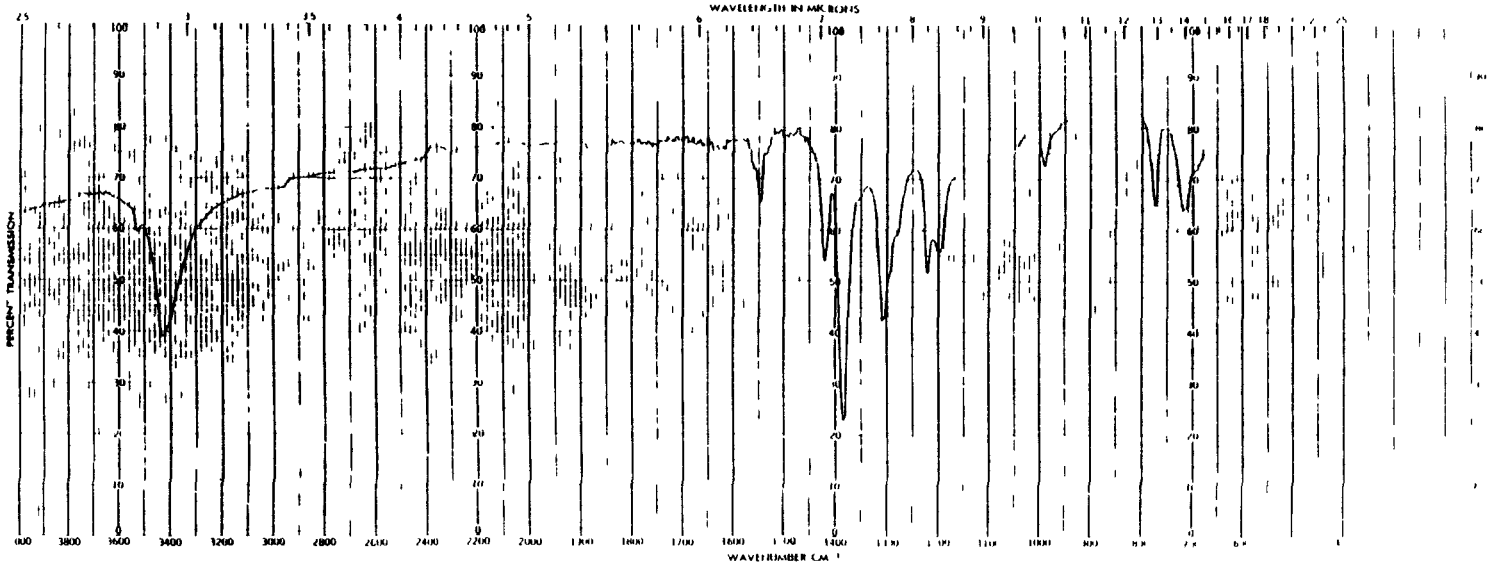


FIGURE 7. INFRARED ABSORPTION SPECTRUM OF PURE PENTACHLOROPHENOL (LOT NO. AC102777)

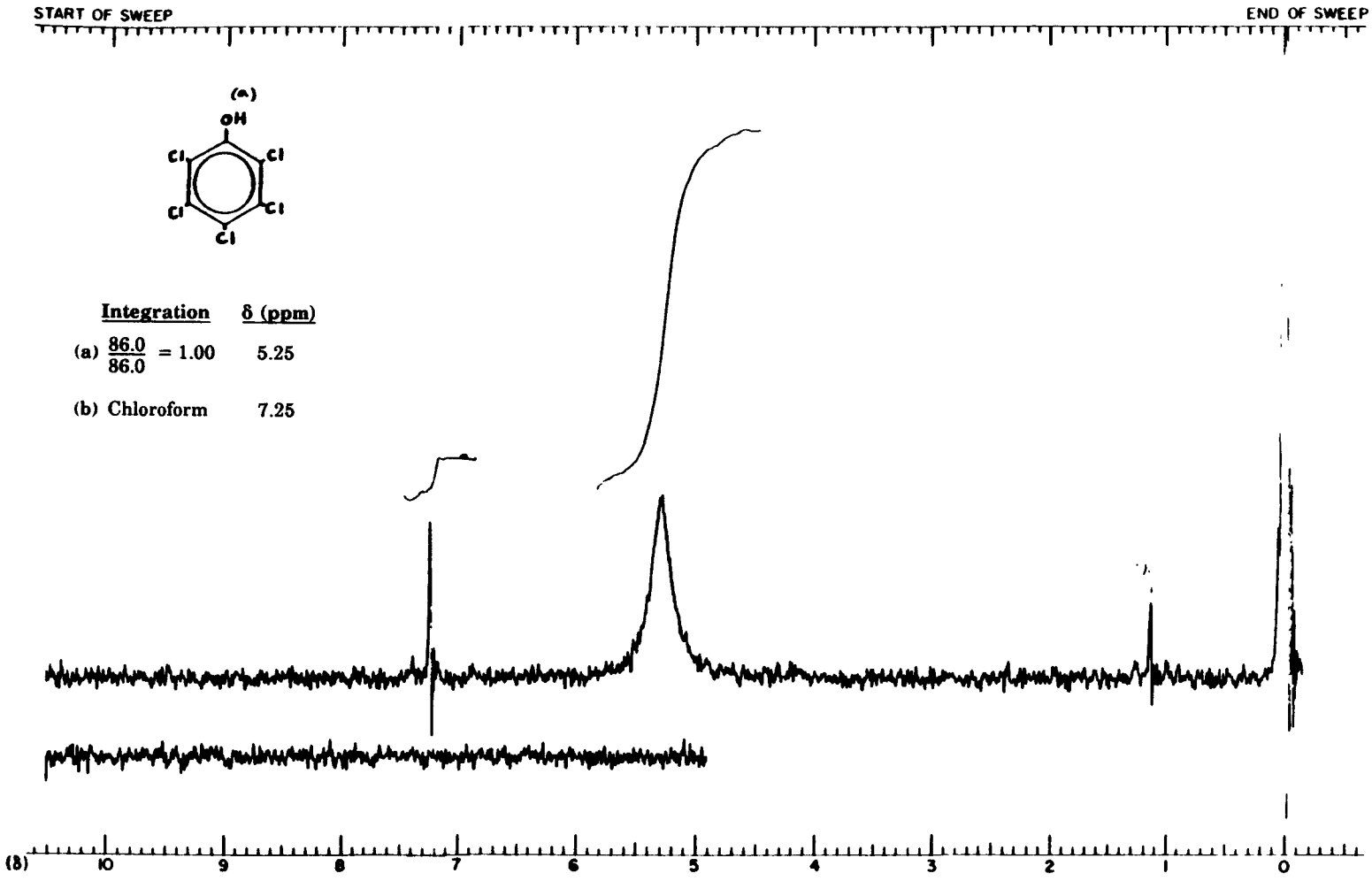


FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PURE PENTACHLOROPHENOL (LOT NO. AC102777)

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diets for the four grades of pentachlorophenol were prepared by adding a dry premix of feed and study chemical to the appropriate amount of feed (Table 4). The mixture was blended for 15 minutes. The homogeneity of diet mixtures formulated at the analytical chemistry and study laboratories was evaluated by extracting feed samples (taken from three locations in the blender) with toluene (at the analytical chemistry laboratory) or with methanol containing 1% hydrochloric acid (at the study laboratory) and analyzing the extract by gas chromatography with a 1% SP1240 DA column, a nitrogen carrier at a flow rate of 30 ml/minute, and electron capture detection. At the analytical chemistry laboratory, studies conducted with the technical-grade material at a concentration of 20 or 2,500 ppm showed deviations of less than 5% from the target concentration At the study laboratory, results of several homogeneity analyses from the 30-day and 6-month studies were outside the ±5% specifications (Table 5). The procedure for the preparation of the feed premix was changed by adding feed flour to the premix for the 2-year studies, and good homogeneity was found during these studies

Analysis at the analytical chemistry laboratory with the same toluene extraction and gas chromatographic system indicated that technical-grade pentachlorophenol, at concentrations of 20 or 2,500 ppm, was stable in feed for 2 weeks at temperatures up to 5° C, with an extraction solvent of 1% hydrochloric acid in methanol, a recovery of greater than 90% was found after storage of feed mixtures containing 20 ppm pentachlorophenol for 2 weeks at 45° C Formulated diets were stored at 4° C for no longer than 2 weeks.

Periodic analyses for pentachlorophenol in feed mixtures were conducted by the study and analytical chemistry laboratories using the 1% hydrochloric acid in methanol extraction and the same gas chromatographic quantitation step. Formulated diets were analyzed once during the 30-day studies, with results ranging from 66% to 104% of the target concentrations for the technical-grade material, 86% to 97% for Dowicide EC-7, and 93% to 104% for pure pentachlorophenol (Table 6) Formulated diets were analyzed twice during the 6-month studies. The results ranged from 94% to 101% for the technical-grade material, 93% to 144% for Dowicide EC-7, 93% to 98% for pure pentachlorophenol, and 94% to 108% for DP-2 (Table 7) During the 2-year studies, the formulated diets were analyzed

TABLE 4. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF PENTACHLOROPHENOL

Thirty-Day Studies (a)	Six-Month Studies (b)	Two-Year Studies (c)
Preparation		
Weighed portion of chemical mixed with 150 g feed for 5 min in a Sorvall Omni mixer; premix combined with additional feed in a twin-shell blender and blended for 15 min	Same as 30-d studies except intensifier bar used	Chemical ground in a mortar with a pestle and passed through a 100-mesh sieve, ground chemical weighed and mixed with feed in a glass beaker with a spatula, premix placed between two layers of remaining feed in a twin-shell blender and blended for 15 min, with the intensifier bar in operation for first 5 min
Maximum Storage Time		
2 wk	2 wk	2 wk
Storage Conditions		
4° ± 2° C in polypropylene buckets	Same as 30 d studies	Same as 30-d studies

(a) Dowicide EC-7 and technical-grade and pure pentachlorophenol
(b) Dowicide EC-7, DP-2, and technical-grade and pure pentachlorophenol
(c) Dowicide EC 7 and technical-grade pentachlorophenol

TABLE 5. RESULTS OF HOMOGENEITY ANALYSIS OF FORMULATED DIETS IN THE FEED STUDIES OF PENTACHLOROPHENOL

Study	Date Mixed	Target Concentration (ppm)	Determined Concentration as Percent of Target (a)
Technical Grade			
Thirty-Day	Not available	20	(b) 48.2-98.1
		12,500	94.1-104.8
Six-Month	06/10/80	200	(b) 85.4-105.1
		1,800	95.2-104.6
Two-Year	04/07/82	100	103.6-109.0
	07/19/83	100	93.4-98.5
Dowicide EC-7			
Thirty-Day	Not available	20	(b) 78.8-129.9
		12,500	(b) 85.0-93.0
Six-Month	06/10/80	200	(b) 86.9-241.1
		1,200	92.6-93.6
	09/17/80	200	95.5-108.5
Two-Year	11/28/83	100	95.2-101.0
		600	94.1-96.6
Pure			
Thirty-Day	Not available	20	(b) 85.8-102.4
		12,500	(b) 87.0-105.0
Six-Month	06/10/80	200	95.2-101.5
		1,500	90.9-95.9
DP-2			
Six-Month	06/11/80	200	(b) 88.0-101.1
		1,200	94.5-96.3

(a) Range of values obtained from three locations in the blender
(b) Out of specifications

TABLE 6. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTY-DAY FEED STUDIES OF PENTACHLOROPHENOL

Study	Target Concentration (ppm) (a)	Determined Concentration (ppm) (b)	Percent of Target
Technical Grade	20	(c) 14.35	(d) 71.75
	100	66.26	(d) 66.26
	500	486.50	97.30
	2,500	2,608.25	104.33
	12,500	(c) 12,584.17	100.67
Dowicide EC-7	20	(c) 19.42	97.10
	100	85.97	(d) 85.97
	500	468.20	93.64
	2,500	2,437.00	97.48
	12,500	(c) 11,051.67	(d) 88.41
Pure	20	(c) 18.68	93.40
	100	101.95	101.95
	500	521.35	104.27
	2,500	2,427.50	97.10
	12,500	(c) 11,771.67	94.17

(a) Formulated diets mixed during week 1
(b) Results of duplicate analysis
(c) Average of values obtained from three locations in the blender
(d) Out of specifications

TABLE 7. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL

Study	Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm) (a)	Percent of Target
Technical Grade	06/10/80	200	(b) 187.7	93.85
		600	607.8	101.30
		1,800	(b) 1,815.3	100.85
	09/16/80	200	189.0	94.95
		600	593.0	98.83
		1,800	1773.0	98.50
Dowicide EC-7	06/10/80	200	(b) 287.8	(c) 143.90
		600	579.6	96.60
		1,200	(b) 1,115.4	93.00
	09/17/80	200	(b) 200.3	100.15
		600	625.0	104.17
		1,200	1,190.0	99.17
Pure	06/10/80	200	(b) 195.4	97.70
		500	486.0	97.20
		1,500	(b) 1,400.0	93.33
	09/16/80	200	189.0	94.50
		500	488.0	97.60
		1,500	1,409.0	93.93
DP-2	06/10/80	200	(b) 188.3	94.15
		600	561.6	93.6
		1,200	(b) 1,141.4	95.12
	09/17/80	200	186.0	93.00
		600	626.0	104.33
		1,200	1,297.0	108.08

(a) Results of duplicate analysis
(b) Average of values obtained from three locations in the blender
(c) Out of specifications

approximately every 8 weeks. In the studies of technical-grade pentachlorophenol, concentrations varied from 0% to 108% of the target concentrations; the second lowest concentration was 91% (Table 8). In the studies of Dowicide EC-7, concentrations varied from 93% to 109% of the target concentrations (Table 9). Because 25/26 analyzed feed mixtures of the technical-grade material were within 10% of the target concentrations, the feed mixtures were estimated to have been within specifications 96% of the time throughout the studies of technical-grade pentachlorophenol. Because 42/42 analyzed feed mixtures of Dowicide EC-7 were within 10% of the target concentrations, the feed mixtures were estimated to have been within specifications throughout the studies of Dowicide EC-7. Referee analyses were periodically performed by the study and analytical chemistry laboratories during the 6-month and 2-year studies. Variable agreement was found between laboratories during the 6-month and early part of the 2-year studies (Table 10), which is attributed to the mixing/homogeneity problems at the study laboratory. These problems were resolved by improving the feed premix procedure to include the use of feed flour obtained by sieving a small amount of the rodent feed through a USS No. 100 sieve (Kuhn et al., 1984).

TABLE 8. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL

Date Mixed	Concentration of Technical-Grade Pentachlorophenol in Feed for Target Concentration (ppm) (a) 100	200
04/07/82	(b) 105.7	199.4
06/08/82	99.8	215.4
08/04/82	103.5	208.5
09/29/82	99.4	202.6
11/22/82	94.4	187.9
01/26/83	90.9	212.8
03/15/83	108.3	211.9
05/03/83	100.7	197.0
07/19/83	(b) 96.1	209.1
08/23/83	99.0	188.0
10/18/83	(c) 0.0	192.2
10/25/83	(d) 100.6	--
01/04/84	91.4	195.3
02/22/84	95.8	196.8
Mean (ppm)	91.2	201.3
Standard deviation	27.87	9.47
Coefficient of variation (percent)	30.6	4.7
Range (ppm)	0-108.3	187.9-215.4
Number of samples	13	13

(a) Results of duplicate analysis
(b) Average of values obtained from three locations in the blender
(c) Out of specifications; not used in the studies. If this value is excluded from the statistical analysis, the mean and standard deviation are 98.8 and 5.37.
(d) Remix; not included in the mean.

TABLE 9. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL, DOWICIDE EC-7

Date Mixed	Concentration of Dowicide EC-7 in Feed for Target Concentration (ppm) (a) 100	200	600
05/05/82	107.8	196.9	615.4
05/11/82	102.9	199.8	633.9
06/30/82	100.9	196.7	560.2
08/24/82	95.5	203.2	607.1
10/19/82	98.5	206.6	587.4
12/14/82	105.6	211.5	593.3
02/01/83	95.2	204.2	597.5
03/21/83	99.5	204.3	605.3
05/31/83	98.7	185.9	607.1
08/22/83	93.8	191.3	601.7
09/26/83	105.6	196.1	611.1
11/28/83	(b) 98.2	206.9	(b) 571.7
01/23/84	109.2	211.9	594.2
03/13/84	99.4	199.0	564.7
Mean (ppm)	100.8	201.0	596.5
Standard deviation	4.79	1.97	20.27
Coefficient of variation (percent)	4.8	1.0	3.4
Range (ppm)	93.8-109.2	185.9-211.9	560.2-633.9
Number of samples	14	14	14

(a) Results of duplicate analysis
(b) Average of values obtained from three locations in the blender

TABLE 10. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE FEED STUDIES OF PENTACHLOROPHENOL

Study	Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
			Study Laboratory (a)	Referee Laboratory (b)
Six-Month				
Technical grade	09/16/80	200	189.0	222
Dowicide EC-7	09/17/80	1,200	1,190.0	1,385
Pure	09/16/80	200	189.0	233
DP-2	09/17/80	600	626.0	776
Two-Year				
Technical grade	04/07/82	100	(c) 105.7	94.7
	11/22/82	200	187.9	237
	01/26/83	200	212.8	178
	10/25/83	100	100.6	104
	02/22/84	200	196.8	205
Dowicide EC-7	05/05/82	100	107.8	92.0
	12/14/82	600	593.3	713
	05/31/83	200	185.9	212
	11/28/83	600	571.7	590
	03/13/84	200	199.0	197

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) Average of values obtained from three locations in the blender

THIRTY-DAY STUDIES

Male and female B6C3F$_1$ mice were obtained from Harlan Industries and held for 16-20 days before the studies began. The animals were 8-9 weeks old when placed on study. Groups of 19 male mice and 15 female mice were fed diets containing 20, 100, 500, 2,500, or 12,500 ppm technical-grade pentachlorophenol for 30 consecutive days. Groups of 19 male mice and 5 female mice were fed diets containing 20, 100, 500, 2,500, or 12,500 ppm Dowicide EC-7 or pure pentachlorophenol according to the same schedule. Groups of 19 male mice and 11 female mice received control diets consisting of Purina Rodent Chow®.

The mice were identified by ear tag and were housed 4-6 per cage. Feed and water were available ad libitum. The mice were observed two times per day and weighed 1 or 5 days before dosing and once per week thereafter. Body temperature was measured weekly with a digital microprobe thermometer (model BAT-8, Bailey Instruments, Inc.) and a rectal probe (no. RET-3). Further details on animal maintenance are given in Table 11.

Five males and five females per dosed group for each of the three grades of pentachlorophenol and five control mice of each sex were placed in a subgroup designated the histopathology/hematology/clinical chemistry group. Groups of eight control and four dosed male mice were assigned to the biochemistry subgroup. The remaining groups of 6 control and 10 dosed male mice for each grade of pentachlorophenol and 6 control and 6 dosed female mice for technical-grade pentachlorophenol were assigned to subgroups that were subsequently terminated without further analysis; body weight and temperature measurements for these subgroups were recorded.

Approximately 1 week before they were killed, mice in the histopathology/hematology/clinical chemistry group were placed in metabolism cages and urine was collected for 24 hours. Urine samples were analyzed for pH, protein, glucose, ketones, bilirubin, occult blood, and specific gravity.

TABLE 11. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PENTACHLOROPHENOL

Thirty-Day Studies	Six-Month Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
19 males/group--5 dosed and 5 controls for the clinical chemistry/histopathology/ hematology subgroups; 4 dosed and 8 controls for biochemistry subgroups; 5 females/dosed group for Dowicide EC-7 or pure pentachlorophenol; 11 or 15 females/ group--5 dosed and 5 controls for clinical chemistry/histopathology/hematology subgroups; 10 dosed and 6 controls of each sex were designated for studies that were later terminated without special analyses; body weight and temperature measurements were made on all mice	25 dosed or 48 control males/group--10 dosed or 10 controls in the behavioral/ histopathology/clinical chemistry subgroups; 4 dosed or 8 controls in the biochemistry subgroups; 6 dosed or 15 controls in the immunology subgroups; 5 dosed or 15 controls in the plaque subgroups; an additional 50 control males were used for baseline determinations in the plaque test; 10 dosed or 10 control females in the behavioral/histopathology/clinical chemistry groups	50 dosed or 35 controls of each sex
Doses		
0, 20, 100, 500, 2,500, or 12,500 ppm pure pentachlorophenol, technical-grade pentachlorophenol, or pentachlorophenol, Dowicide EC-7, in feed	0, 200, 500, or 1,500 ppm pure pentachlorophenol in feed; 0, 200, 600, or 1,800 ppm technical-grade pentachlorophenol in feed; 0, 200, 600, or 1,200 ppm pentachlorophenol, Dowicide EC-7 in feed, or 0, 200, 600, or 1,200 ppm pentachlorophenol, DP-2, in feed	0, 100, or 200 ppm technical-grade pentachlorophenol in feed; 0, 100, 200, or 600 ppm pentachlorophenol, Dowicide EC-7, in feed
Date of First Dose		
Histopathology/clinical chemistry and biochemistry subgroups--6/15/79; other animals--6/19/79	Male: behavioral/histopathology/clinical chemistry--6/16/80; biochemistry--6/9/80; immunology--6/2/80; plaque--6/23/80; female: 6/9/80	Technical-grade pentachlorophenol--4/14/82; Dowicide EC-7--5/12/82
Date of Last Dose		
Histopathology/clinical chemistry and biochemistry subgroups--7/14/79; other animals--7/18/79	Male: behavioral/histopathology/clinical chemistry--12/17/80-12/19/80; biochemistry--12/8/80-12/12/80; immunology--12/1/80-12/5/80; plaque--12/22/80	Technical-grade pentachlorophenol--4/4/84; Dowicide EC-7--5/2/84
Duration of Dosing		
30 d	Male--26 wk; female--27 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 or 5 d before dosing and 1 × wk thereafter; feed consumption measured 2 × wk	Observed 2 × d; weighed initially and 1 × wk thereafter; feed consumption measured 2 × wk	Observed 2 × d; weighed 1 × wk for 12 or 13 wk and 1 × mo thereafter; feed consumption measured 1 × mo
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all animals in the histopathology/clinical chemistry subgroups; histologic exam performed on all controls, all animals in the highest surviving dosed group, and animals dying before termination. Tissues examined include: accessory sex organs/testes or ovaries/uterus, adrenal glands and pituitary gland, brain, cecum, colon, duodenum, ear canal, esophagus, gross lesions and tissue masses with regional lymph nodes, heart and aorta, ileum, larynx, liver, lungs, mammary gland, mesenteric and thoracic lymph nodes, nasal turbinates, pancreas, parathyroid glands, quadriceps, right eye,	Necropsy performed on all animals in the behavior/histopathology/clinical chemistry groups; histologic exam performed on all controls, all high dose animals, all animals in the 600-ppm technical-grade pentachlorophenol groups, and all animals dying before the end of the studies. Tissues examined include: adrenal glands, brain, cecum, colon, duodenum, ear canal, esophagus, eyes, gross lesions, heart and aorta, ileum, kidneys, larynx, liver, lumbar spinal cord, lungs, mammary gland, mesenteric and thoracic lymph nodes, nasal turbinates,	Necropsy performed on all animals; the following tissues were examined histologically for all control and high dose animals: adrenal glands, brain, colon, esophagus, eyes if grossly abnormal, gallbladder, gross lesions and tissue masses with regional lymph nodes, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spleen, stomach, thymus, thyroid gland, trachea,

TABLE 11. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Thirty-Day Studies	Six-Month Studies	Two-Year Studies
Necropsy, Histologic Examinations, and Supplemental Studies (Continued)		
right kidney, right pinna, salivary glands, sciatic nerve, skin lesions if present, spinal cord (lumbar region), spleen, sternum including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder; organ weights obtained at necropsy include: adrenal glands, brain, heart, liver, lungs, right kidney, spleen, testis or ovary/uterus, and thymus; supplemental studies include: aryl hydrocarbon hydroxylase, body temperature, clinical chemical analysis, hematologic analysis, liver porphyrins, oxidative phosphorylation, cytochrome P450, and urinalysis	pancreas, parathyroid glands, pinna, pituitary gland, prostate/seminal vesicles/testes or ovaries/uterus, quadriceps, salivary glands, sciatic nerve, spleen, sternum including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder. Liver, nasal turbinates (except for 200-ppm males), and urinary bladder examined for 200- and 500-ppm pure pentachlorophenol groups; liver, lungs, and urinary bladder examined for the 200-ppm technical-grade pentachlorophenol groups; liver, nasal turbinates (except for 200-ppm males), and urinary bladder examined for the 200- and 600-ppm Dowicide EC-7 groups; liver, spleen (males only), and urinary bladder examined for the 200- and 600-ppm DP-2 groups; supplemental studies include: aryl hydrocarbon hydroxylase, behavior, body temperature, clinical chemical analysis, hematologic analysis, immunologic analysis, oxidative phosphorylation, cytochrome P450, plaque test, porphyrins, and urinalysis	urinary bladder, and vertebrae, sternebrae, or femur including marrow; adrenal glands, gross lesions, and liver examined from other dose groups
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species $B6C3F_1$ mice	$B6C3F_1$ mice	$B6C3F_1$ mice
Animal Source Harlan Industries (Indianapolis, IN)	Harlan Industries (Indianapolis, IN) or Charles River Breeding Laboratories (Kingston, NY); all Charles River animals assigned to the plaque test	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification Ear tag	Ear tag	Toemark and earmark
Time Held Before Study 16-20 d	10-19 d	22 d
Age When Placed on Study 8-9 wk	7-9 wk	9 wk
Age When Killed 13 wk	34 wk	112 wk
Necropsy Dates 7/16/79-7/18/79	Pure pentachlorophenol--12/15/80-12/17/80; DP-2--12/17/80-12/19/80; technical-grade pentachlorophenol--12/15/80-12/18/80; Dowicide EC-7--12/16/80-12/19/80	Technical-grade pentachlorophenol--4/11/84-4/13/84; Dowicide EC-7--5/7/84-5/10/84

TABLE 11. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Thirty-Day Studies	Six-Month Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Method of Animal Distribution		
Distributed to weight classes and assigned to groups according to a table of random numbers	Distributed to weight classes and assigned to groups according to a table of random numbers	Animals distributed to weight classes and assigned to cages according to one table of random numbers and to groups by another table of random numbers
Feed		
Purina Rodent Chow® meal (Ralston Purina, St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 6-mo studies
Bedding		
Absorb-Dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as 30-d studies	Same as 30-d studies
Water		
8-oz glass water bottles and stoppers; available ad libitum	Same as 30-d studies	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum
Cages		
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 30-d studies	Same as 30-d studies
Cage Filters		
Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 30-d studies	Same as 30-d studies
Cage Rotation		
No	No	Yes
Animals per Cage		
4-6	3-5	5 (males housed individually after 16 mo: 8/3/83)
Chemicals on Study in the Same Room		
Pure pentachlorophenol, technical-grade pentachlorophenol, Dowicide EC-7	Pure pentachlorophenol, technical-grade pentachlorophenol, Dowicide EC-7, DP-2	Technical-grade pentachlorophenol, Dowicide EC-7
Animal Room Environment		
Temp--70°-74° F; hum--40%-60%; fluorescent light 12 h/d; at least 15 room air changes/h	Same as 30-d studies	Temp--54°-78° F; hum--23%-77%; fluorescent light 12 h/d; at least 15 room air changes/h

One or two days before the mice in the histopathology/hematology/clinical chemistry group were killed, blood was withdrawn from the orbital plexus and analyzed for hemoglobin concentration, hematocrit value, total and differential leukocyte count, erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, and reticulocyte count. On the day the mice in the histopathology/clinical chemistry group were killed, they were anesthesized with sodium pentobarbital and blood samples were withdrawn by cardiac puncture. The following analyses were performed: alkaline phosphatase, serum glutamic-pyruvic transaminase, γ-glutamyl transpeptidase, bilirubin, cholesterol, triglycerides, blood urea nitrogen, glucose, total protein, and the proportions of albumin and globulins. The methods of analysis are similar to those described in Appendix H.

A necropsy was performed on all animals in the histopathology/clinical chemistry group except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 11.

The following organs were weighed: lungs, heart, liver, spleen, thymus, right kidney, brain, adrenal glands, right testis, right ovary, and uterus. Liver samples were analyzed for porphyrin content by the method of Abbritti and DeMatteis (1971-1972). Liver and right kidney samples were inspected for fluorescence under ultraviolet light.

Biochemistry studies were performed on four male mice per dosed group for each of the three grades of pentachlorophenol and on eight male mice in the control group; four of the control mice were given an intraperitoneal injection of 1 mg of 3,4-benzo[*a*]pyrene 24 hours before they were killed and served as positive controls for aryl hydrocarbon hydroxylase (AHH) determination (Appendix H). The liver of these animals was removed and analyzed for AHH activity, cytochrome P450 content, and uncoupling of oxidative phosphorylation.

SIX-MONTH STUDIES

Six-month studies were conducted to evaluate the cumulative toxic effects of repeated administration of four grades of pentachlorophenol and to determine the concentrations to be used in the 2-year studies.

Five- to six-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries or Charles River Breeding Laboratories and were observed for 10-19 days. Animals were distributed to weight classes; animals were assigned to cages and cages to groups according to tables of random numbers.

Groups of 25 male mice and 10 female mice were given diets containing 200, 600, or 1,800 ppm technical-grade pentachlorophenol; 200, 600, or 1,200 ppm Dowicide EC-7; 200, 600, or 1,200 ppm DP-2; or 200, 500, or 1,500 ppm pure pentachlorophenol for 26-27 weeks. Ninety-eight male mice (distributed to various control groups; see below) and 10 female mice were fed control diets consisting of NIH 07 Rat and Mouse Ration. Formulated or control diets and water were available ad libitum. Further experimental details are summarized in Table 11.

Animals were checked two times per day; moribund animals were killed. Feed consumption was measured two times per week. Individual animal weights were recorded once per week. Body temperatures (rectal) were measured during weeks 9 and 26.

Mice dosed with the four grades of pentachlorophenol and control mice were separated into subgroups designated the behavior, histopathology, hematology, and clinical chemistry group (core group); biochemistry group; immunology group; and plaque test group. The number of mice in each subgroup is given in Table 11.

Behavioral studies and body temperature measurements were performed on mice in the core group during weeks 5 and 26. Studies included examination for presence or absence of autonomic signs; pinnal, corneal, and righting reflexes; spontaneous motor activity; acoustical startle response; visual placement response; grip strength; and rotarod testing. Methods for the behavioral studies are given in Appendix H.

During the final week of the studies, mice in the core group were placed in metabolism cages and urine was collected for 24 hours. Samples were

analyzed for appearance and color, specific gravity, and creatinine. One or two days before the mice in the core group were killed, blood was withdrawn from the orbital plexus and analyzed for hemoglobin concentration, hematocrit value, total and differential leukocyte counts, erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, and reticulocyte count. On the day the mice in the core group were killed, they were anesthetized with sodium pentobarbital and blood samples were withdrawn by cardiac puncture. The following analyses were performed: alkaline phosphatase, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, γ-glutamyl transpeptidase, cholesterol, creatinine, and total protein. Analytical procedures are given in Appendix H.

At the end of the 6-month studies, a necropsy was performed on all animals in the core group except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 11. Liver, spleen, brain, and thymus were weighed; the liver and both kidneys were examined for fluorescence. Liver porphyrins were determined by the method of Abbritti and DeMatteis (1971-1972); urinary porphyrins were determined by the method of Henry et al. (1974) (Appendix H).

At the end of the 6-month studies, the liver from mice in the biochemistry group was removed and analyzed for AHH activity (Gielen et al., 1972), cytochrome P450 content (Omura and Sato, 1964), and uncoupling of oxidative phosphorylation (Friedman et al., 1977) (Appendix H). Four mice that served as positive controls for the AHH determination were given an intraperitoneal injection of 1 mg 3,4-benzo[a]pyrene 24 hours before they were killed.

At the end of the 6-month studies, mice in the immunology group were killed, and the thymus and spleen were removed. Effects on T-cells were assessed by the response of thymic and splenic lymphocytes to the mitogens concanavalin A and phytohemagglutinin. Effects on B-cells were assessed by the response of splenic lymphocytes to pokeweed mitogen.

Mice in the plaque test group were given intraperitoneal injections of sheep erythrocytes 9 days before the end of the 6-month studies (Appendix H). At the end of the studies, mice were anesthesized with ether, blood was obtained by cardiac puncture, and the spleen was removed. Humoral immune competence was assessed by measurement of the plaque-forming cell response and serum hemagglutination titers.

TWO-YEAR STUDIES

Study Design

Diets containing 100 or 200 ppm technical-grade pentachlorophenol or 100, 200, or 600 ppm Dowicide EC-7 were fed to groups of 50 male and 50 female mice. Two groups of 35 male and 35 female mice were fed control diets.

Source and Specifications of Animals

The male and female $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Mice were shipped to the study laboratory at 6 weeks of age. The animals were quarantined at the study facility for 22 days. Thereafter, a complete necropsy was performed on five mice of each sex to assess their health status. The mice were placed on study at 9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage until month 16, after which time males were housed individually because of fighting. Feed and water were available ad libitum. Cages were rotated on the racks every 2 weeks. Further details of animal maintenance are given in Table 11.

Clinical Examinations and Pathology

All animals were observed two times per day, and abnormal clinical signs were recorded when observed. Body weights were recorded once per week for the first 12 or 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned at 6 µm, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (see Table 11) were performed on all high dose and control animals and on lower dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose groups were examined histopathologically. If mortality in the highest dose group exceeded that in the control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974) (body weight and feed consumption) or Toxicology Data Management System (survival and pathology). The data elements include descriptive information on the chemicals, animals, experimental design, survival, and individual pathology results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or 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 the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic 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 histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed. The incidences of various lesions in the two control groups (35 animals each) were combined, when appropriate, to add statistical power.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data: life table tests, logistic regression, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of each dosed group with controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--This method of analysis assumes that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Logistic Regression Analyses--This method of analysis assumes that all tumors of a given type were "incidental"; i.e., they did not alter the risk of death and were discovered merely as the result of death from an unrelated cause. According to this approach, tumor prevalence was modeled as a logistic function of dose 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 dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986).. If the tumor type is nonlethal, this comparison of the time-specific tumor prevalence also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984). As a supplemental procedure, additional analyses were conducted by comparing the tumor incidences in

dosed groups with that in the combined control group from the technical-grade pentachlorophenol and Dowicide EC-7 studies. Only time-adjusted tests were considered, so the substantial difference in survival between the two control groups was compensated for by the statistical procedures.

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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 tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

Analysis of Continuous Variables: For the organ weight and the hematologic, serum chemistry, biochemistry, and urinalysis data from the 6-month studies, nonparametric multiple comparison procedures of Dunn (1964) and Shirley (1977) were used to assess the significance of pairwise differences between dosed and control groups. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends.

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in a series (four strains used) or in a hierarchy (initial testing in TA98 and TA100; if results were negative, then the chemical was tested further in additional strains). If all results were negative, the chemical was retested in all strains with a different concentration of S9.

Each test consisted of three plates each of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, Texas). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations 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 (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited

by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more 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 the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 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.

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. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

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 usually scored for frequency of SCEs per cell from each dose; 100 (more recently, 200) first-division metaphase cells were scored at each dose for the chromosomal aberration 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. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P < 0.003$) effect on the slope of the curve or on a dose point ($P < 0.05$) was sufficient for a conclusion of positive for a test.

III. RESULTS

MICE

THIRTY-DAY STUDIES

SIX-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

THIRTY-DAY STUDIES

Fourteen of 19 male mice and 7/15 female mice that received 12,500 ppm technical-grade pentachlorophenol died before the end of the studies (Table 12); final mean body weights of males and females that received 12,500 ppm were 38% and 28% lower than those of controls.

All mice that received 12,500 ppm EC-7 and 9/19 males and 1/5 females that received 2,500 ppm were dead by day 4 (Table 13). The final mean body weight of mice that received 2,500 ppm was 13% lower than that of controls for males and 10% lower for females; final mean body weights of mice in all other dosed groups were comparable to those of controls.

TABLE 12. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTY-DAY FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)
MALE						
0	19/19	25.0	29.9	+4.9		5.8
20	19/19	26.0	31.0	+5.0	103.7	5.6
100	19/19	25.7	30.9	+5.2	103.3	5.6
500	19/19	26.6	31.5	+4.9	105.4	6.1
2,500	19/19	25.5	28.4	+2.9	95.0	5.7
12,500	(e) 5/19	26.1	18.4	−7.7	61.5	7.9
FEMALE						
0	11/11	19.2	22.2	+3.0		5.5
20	15/15	19.6	23.3	+3.7	105.0	5.6
100	15/15	19.5	22.9	+3.4	103.2	5.9
500	15/15	19.1	23.0	+3.9	103.6	5.9
2,500	15/15	18.9	22.4	+3.5	100.9	5.3
12,500	(f) 8/15	18.5	15.9	−2.6	71.6	4.9

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the group
(d) Grams per animal per day averaged over the 4-week period; not corrected for scatter.
(e) Day of death: 2,2,2,2,2,4,4,4,22,26,26,26,26,30
(f) Day of death: 2,2,4,24,28,30,30

TABLE 13. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTY-DAY FEED STUDIES OF PENTACHLOROPHENOL, DOWICIDE EC-7

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)
MALE						
0	19/19	25.0	29.9	+4.9		5.8
20	19/19	25.2	30.1	+4.9	100.7	6.1
100	19/19	24.4	29.4	+5.0	98.3	5.6
500	19/19	25.7	31.3	+5.6	104.7	5.9
2,500	(e) 10/19	25.4	26.1	+0.7	87.3	10.5
12,500	(f) 0/19	24.1	(g)	(g)	(g)	(g)
FEMALE						
0	11/11	19.2	22.2	+3.0		5.5
20	5/5	18.2	21.2	+3.0	95.5	5.7
100	5/5	19.4	23.3	+3.9	105.0	6.0
500	5/5	18.4	22.8	+4.4	102.7	5.8
2,500	(h) 4/5	13.6	20.0	+6.4	90.1	5.7
12,500	(i) 0/5	17.4	(g)	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the group
(d) Grams per animal per day averaged over the 4-week period; not corrected for scatter.
(e) Day of death: all 4
(f) Day of death: 10 on day 2; 9 on day 4
(g) No data are reported due to 100% mortality in this group.
(h) Day of death: 4
(i) Day of death: 2,2,4,4,4

All mice that received 12,500 ppm pure pentachlorophenol and 2/19 males that received 2,500 ppm died before the end of the studies (Table 14). The final mean body weight of mice that received 2,500 ppm was 10% lower than that of controls for males and 5% lower for females.

Weakness, lethargy, and shallow breathing were observed within 24-48 hours of initial exposure, followed by severe weight loss, convulsions, and death for mice that received 12,500 ppm of the three grades of pentachlorophenol. Similar but less marked effects were observed in surviving mice that received 12,500 ppm technical-grade or pure pentachlorophenol or 2,500 ppm EC-7. Feed consumption by all dosed groups was generally comparable to that by controls.

TABLE 14. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTY-DAY FEED STUDIES OF PURE PENTACHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d)
MALE						
0	19/19	25.0	29.9	+4.9		5.8
20	19/19	25.6	30.0	+4.4	100.3	6.1
100	19/19	25.1	30.0	+4.9	100.3	6.4
500	19/19	26.6	31.0	+4.4	103.7	5.8
2,500	(e) 17/19	26.0	27.0	+1.0	90.3	6.4
12,500	(f) 0/19	25.8	(g)	(g)	(g)	(g)
FEMALE						
0	11/11	19.2	22.2	+3.0		5.5
20	5/5	19.4	22.8	+3.4	102.7	6.6
100	5/5	19.2	22.6	+3.4	101.8	5.5
500	5/5	19.0	22.4	+3.4	100.9	5.5
2,500	5/5	19.8	21.0	+1.2	94.6	5.3
12,500	(h) 0/5	19.4	(g)	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the group
(d) Grams per animal per day averaged over the 4-week period; not corrected for scatter.
(e) Day of death: 4,4
(f) Day of death: 12 on day 2; 6 on day 4; 1 on day 6
(g) No data are reported due to 100% mortality in this group.
(h) Day of death: 4,4,12,24,24

Body temperatures (rectal) were decreased by 1°-2° C in most of the groups (male and female) that received 12,500 or 2,500 ppm (Table 15). The effect was seen at 12,500 ppm as early as week 1 and was seen starting at week 2 in the 2,500-ppm groups. After its first appearance, the reduced body temperature did not progress or regress in severity during the remainder of the studies. Males and females appeared to be equally affected, and the effect was similar for all three grades of pentachlorophenol.

Mean liver weights and liver to body weight ratios were significantly increased for mice fed each of the three grades of pentachlorophenol at the higher concentrations (data available at the NTP). Spleen and thymic weights and spleen to body weight ratios were significantly reduced for males that received 2,500 or 12,500 ppm technical-grade pentachlorophenol. Results of analysis of other organ weight data were sporadically significant without a dose-related trend or an indication of a compound-related effect.

Increases in mean serum alkaline phosphatase, cholesterol, and serum glutamic-pyruvic transaminase values were observed for all male and female mice that were exposed to pentachlorophenol (data available at the NTP). Changes in these values were more pronounced in the mid and high dose groups that received technical-grade pentachlorophenol. Serum γ-glutamyl transpeptidase levels were greatly increased for both male and female mice exposed to technical-grade pentachlorophenol at 2,500 or 12,500 ppm.

TABLE 15. MEAN BODY TEMPERATURES FOR MICE IN THE THIRTY-DAY FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Examined (b)	Weeks on Study 1	2	3	4	Mean
MALE						
0	19	36.6 ± 0.5	36.5 ± 0.2	36.0 ± 0.9	36.8 ± 0.6	36.5
Technical Grade						
20	19	36.3 ± 1.2	37.0 ± 0.7	37.2 ± 0.7	37.4 ± 0.4	37.0
100	19	36.4 ± 0.6	36.5 ± 0.4	37.2 ± 1.1	36.6 ± 0.4	36.7
500	19	35.8 ± 0.5	36.5 ± 0.1	36.2 ± 0.7	36.8 ± 0.5	36.3
2,500	19	36.0 ± 0.5	36.0 ± 0.2	35.2 ± 0.4	35.9 ± 0.5	35.8
12,500	11	35.7 ± 0.6	34.3 ± 0.8	34.4 ± 0.4	(c) 34.9 ± 0.6	34.8
Dowicide EC-7						
20	19	35.8 ± 1.0	35.8 ± 0.4	35.5 ± 0.4	36.0 ± 0.8	35.8
100	19	35.8 ± 0.1	36.6 ± 0.8	35.6 ± 0.6	35.9 ± 0.5	36.0
500	19	36.3 ± 0.2	36.2 ± 0.5	35.7 ± 0.3	36.1 ± 0.2	36.1
2,500	10	(d) 35.8 ± 0.6	35.4 ± 0.4	34.8 ± 0.4	36.4 ± 0.4	35.6
12,500	3	34.4 ± 0.0	(e)	(e)	(e)	--
Pure						
20	19	36.0 ± 0.3	36.5 ± 0.4	35.7 ± 0.4	36.0 ± 0.5	36.0
100	19	36.2 ± 0.1	36.2 ± 0.6	35.6 ± 0.7	36.3 ± 0.6	36.1
500	19	36.4 ± 0.5	36.5 ± 0.1	36.0 ± 0.3	36.2 ± 0.1	36.3
2,500	17	35.5 ± 0.4	35.6 ± 0.4	35.0 ± 0.4	35.4 ± 0.4	35.4
12,500	2	34.9 ± 0.1	(e)	(e)	(e)	--
FEMALE						
0	11	37.2 ± 0.4	37.4 ± 0.1	37.0 ± 0.2	37.2 ± 0.4	37.2
Technical Grade						
20	15	36.9 ± 0.8	37.6 ± 0.4	37.0 ± 0.4	37.4 ± 0.5	37.2
100	15	36.8 ± 0.4	37.5 ± 0.2	36.6 ± 0.8	37.4 ± 0.6	37.1
500	15	36.6 ± 0.5	37.3 ± 0.4	36.5 ± 0.4	37.4 ± 0.6	37.0
2,500	15	37.2 ± 0.3	36.8 ± 0.2	36.2 ± 0.2	37.1 ± 0.2	36.8
12,500	11	(d) 35.9 ± 1.1	35.3 ± 1.0	34.4 ± 1.0	35.5 ± 1.8	35.3
Dowicide EC-7						
20	5	37.2 ± 0.3	37.5 ± 0.3	36.6 ± 0.5	37.3 ± 0.7	37.2
100	5	37.4 ± 0.4	37.8 ± 0.3	36.5 ± 0.4	37.7 ± 0.3	37.4
500	5	37.4 ± 0.4	37.1 ± 0.5	37.0 ± 0.7	37.4 ± 0.4	37.2
2,500	4	37.4 ± 0.9	35.5 ± 0.4	36.0 ± 0.9	36.7 ± 0.2	36.4
Pure						
20	5	37.0 ± 0.5	38.4 ± 0.4	37.0 ± 0.4	37.9 ± 0.8	37.6
100	5	37.4 ± 0.3	37.3 ± 0.8	37.1 ± 0.8	37.8 ± 0.4	37.4
500	5	37.3 ± 0.3	37.7 ± 0.6	35.6 ± 1.1	37.1 ± 0.5	36.9
2,500	5	37.8 ± 0.5	36.4 ± 0.8	35.4 ± 0.8	36.2 ± 0.4	36.4
12,500	3	32.0 ± 0.6	31.9 ± 2.8	(f) 32.1 ± 0.1	(e)	32.0

(a) Mean ± standard deviation; rectal temperature recorded in degrees Celsius; common control groups used for all four grades of pentachlorophenol.
(b) Except as noted
(c) Nine animals were examined.
(d) Twelve animals were examined.
(e) No data are reported due to 100% mortality of the group.
(f) Two animals were examined.

Dose-related changes in urine color and appearance were noted for samples collected from both males and females that received the mid or high dose concentration of each pentachlorophenol feed formulation (data available at the NTP). The urine ranged from yellow or dark yellow to brown or dark brown as the concentration of pentachlorophenol in the diets increased. Compared with the values in the controls, compound-related increases in specific gravity values were found for urine samples obtained from mice in each group exposed to pentachlorophenol. No other clearly defined chemical- or dose-related effects were demonstrated for pH, protein, glucose, ketones, or occult blood.

The most distinguishing feature found in the hemograms for males fed each grade of pentachlorophenol was a marked reduction in the leukocyte count (data available at the NTP). This decrease was considered to be clinically significant but was not statistically significant because of the wide variation seen within groups and the low statistical power afforded by the small sample size; the trends appeared to be real, however, and resulted primarily from decreased lymphocyte counts that were also not statistically significant. Mild reductions in lymphocyte counts were also observed in females fed diets containing 500 or 2,500 ppm Dowicide EC-7. Monocytosis was noted for both males and females fed each of three grades of pentachlorophenol; however, these increases were statistically significant only for females given Dowicide EC-7. Platelet counts were occasionally increased, being most prominent in males and females given technical-grade pentachlorophenol. Other hematologic results that were statistically significant were not considered to be biologically significant because they were sporadic or the change was mild and the values were within the normal range.

Induction of liver microsomal aryl hydrocarbon hydroxylase (AHH) activity and increased P450 levels were seen in mice exposed to each of the three grades of pentachlorophenol (data available at the NTP). The total inductive effect was considerably greater with technical-grade pentachlorophenol, which was the only formulation to show a dose-related inductive effect on AHH activity. However, only one mouse, an animal exposed to technical-grade pentachlorophenol, survived at 12,500 ppm. Exposure to either pure pentachlorophenol or technical-grade pentachlorophenol resulted in a dose-related inductive effect on P450 levels.

The effects of the three formulations on mitochondrial oxidative phosphorylation were studied (data available at the NTP). An increase in the incubation concentration of oxygen was seen in animals fed diets containing pure pentachlorophenol, especially at the higher doses, compared with that seen in control animals, indicating reduced consumption of oxygen. A similar effect was observed in animals exposed at lower concentrations of technical-grade pentachlorophenol but was not present in animals dosed at higher concentrations. A slight increase in oxygen concentration was also observed in animals exposed at the lower Dowicide EC-7 concentrations. At the higher concentrations and when pyruvate was the substrate, the oxygen concentration was decreased, indicating increased oxygen consumption and phosphorylation.

Pure pentachlorophenol, especially at high concentrations, decreased the phosphate:oxygen ratio, indicating an uncoupling effect on oxidative phosphorylation. This uncoupling effect was also observed with technical-grade pentachlorophenol at the lower concentrations but disappeared at 2,500 ppm. Only one animal survived exposure at 12,500 ppm; however, there appeared to be an inductive effect at this higher concentration. A decrease in the phosphate:oxygen ratio was seen in mice exposed to Dowicide EC-7 at the lower concentrations and an increase was seen at the higher (2,500 ppm) concentration, except when citrate was used as the substrate. The effect was markedly greater when pyruvate was used as a substrate, indicating that the inductive effect apparently takes place primarily outside the citric acid cycle.

The effects of the three formulations on total liver porphyrins were studied. For some reason, the results for the control animals were higher than would have been expected, based on the results for the low dose animals. Another group of control animals was evaluated for total liver

porphyrins at a later date, and the concentrations of liver porphyrins were found to be considerably lower. However, these latter results were not used, since the animals were not the same age as the dosed animals.

All three formulations increased total liver porphyrins in male mice, but only pure pentachlorophenol and technical-grade pentachlorophenol increased the concentration in female mice. Dowicide EC-7 may even have decreased the liver porphyrin concentration in the 2,500-ppm female mice. A dose-related increased effect could also be observed with technical-grade pentachlorophenol in both male and female mice.

Compound-related liver lesions in mice that received each grade of pentachlorophenol included centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration, or necrosis. These lesions were more diffuse and severe in mice receiving technical-grade pentachlorophenol and were least apparent in mice receiving EC-7 (Table 16).

SIX-MONTH STUDIES

All mice that received 1,800 ppm technical-grade pentachlorophenol died before the end of the studies (Table 17). Final mean body weights of surviving animals were comparable to those of controls.

Two male mice that received 1,200 ppm DP-2 died before the end of the studies (Table 18). Final mean body weights of males and females that received 1,200 ppm were 6% lower than those of controls.

One male mouse that received 200 ppm Dowicide EC-7 died before the end of the studies (Table 19). Final mean body weights of males and females that received 1,200 ppm were 13% and 11% lower than those of controls.

Two male mice that received 200 ppm pure pentachlorophenol died before the end of the studies (Table 20). Final mean body weights of males and females that received 1,500 ppm were 8% and 9% lower than those of controls.

TABLE 16. INCIDENCES OF CYTOMEGALY, KARYOMEGALY, NUCLEAR ATYPIA, DEGENERATION, OR NECROSIS OF THE LIVER IN MICE IN THE THIRTY-DAY FEED STUDIES OF PENTACHLOROPHENOL

Concentration (ppm)	Technical-Grade Pentachlorophenol		Pentachlorophenol, Dowicide EC-7		Pure Pentachlorophenol	
	Male	Female	Male	Female	Male	Female
0	0/5	0/5	0/5	0/5	0/5	0/5
20	(a)	(a)	(a)	(a)	(a)	0/5
100	0/5	0/5	0/5	(a)	0/5	1/5
500	5/5	5/5	2/5	0/5	5/5	5/5
2,500	5/5	4/4	2/3	4/4	4/5	5/5
12,500	2/3	4/4	(a)	(a)	0/5	3/4

(a) Not examined histopathologically

TABLE 17. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE SIX-MONTH FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 8	Week 24
MALE							
0	10/10	26.8 ± 0.4	39.3 ± 1.1	+12.5 ± 1.1		7.9	8.4
200	10/10	27.1 ± 0.3	40.7 ± 0.8	+13.6 ± 0.8	103.6	7.4	8.0
600	10/10	27.7 ± 0.6	40.3 ± 1.3	+12.6 ± 1.4	102.5	19.1	21.3
1,800	(e) 0/10	26.8 ± 0.5	(f)	(f)	(f)	8.2	(f)
FEMALE							
0	10/10	19.3 ± 0.3	31.8 ± 0.7	+12.5 ± 0.7		8.9	9.6
200	10/10	18.6 ± 0.5	32.3 ± 1.0	+13.7 ± 0.8	101.6	8.9	8.0
600	10/10	18.9 ± 0.4	31.7 ± 0.7	+12.8 ± 0.6	99.7	8.8	8.6
1,800	(g) 0/10	19.1 ± 0.3	(f)	(f)	(f)	8.1	16.0

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day (not corrected for scatter); animals were housed in varying numbers per cage with some cages, particularly those with a single occupant, having a high degree of feed wastage.
(e) Week of death: 17,19,19,19,20,20,20,21,21,23
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 19,23,24,24,24,25,26,26,26,26

TABLE 18. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL, DP-2

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 8	Week 24
MALE							
0	10/10	26.8 ± 0.4	39.3 ± 1.1	+12.5 ± 1.1		6.9	8.4
200	10/10	27.0 ± 0.5	42.6 ± 0.9	+15.6 ± 0.8	108.4	7.7	8.4
600	10/10	27.8 ± 0.6	38.1 ± 0.7	+10.3 ± 0.7	96.9	6.1	7.8
1,200	(e) 8/10	29.5 ± 0.6	36.8 ± 1.2	+7.4 ± 0.7	93.6	7.9	16.0
FEMALE							
0	10/10	19.3 ± 0.3	31.8 ± 0.7	+12.5 ± 0.7		8.9	9.6
200	10/10	19.6 ± 0.3	34.2 ± 0.7	+14.6 ± 0.7	107.5	8.0	8.9
600	10/10	19.2 ± 0.4	32.0 ± 0.8	+12.8 ± 0.9	100.6	8.9	8.3
1,200	10/10	18.4 ± 0.3	29.9 ± 0.9	+11.5 ± 0.7	94.0	8.4	7.7

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day (not corrected for scatter); animals were housed in varying numbers per cage with some cages, particularly those with a single occupant, having a high degree of feed wastage.
(e) Week of death: 25,26

TABLE 19. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL, DOWICIDE EC-7

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 8	Week 24
MALE							
0	10/10	26.8 ± 0.4	39.3 ± 1.1	+12.5 ± 1.1		6.9	8.4
200	(e) 9/10	27.1 ± 0.5	41.9 ± 1.3	+14.8 ± 1.0	106.6	6.8	8.4
600	10/10	26.7 ± 0.6	36.6 ± 1.3	+9.9 ± 1.0	93.1	7.3	7.8
1,200	10/10	26.0 ± 0.2	34.3 ± 0.6	+8.3 ± 0.7	87.3	7.7	8.4
FEMALE							
0	10/10	19.3 ± 0.3	31.8 ± 0.7	+12.5 ± 0.7		8.9	9.6
200	(f) 10/10	19.6 ± 0.3	32.7 ± 0.8	+13.1 ± 0.7	102.8	9.2	8.4
600	10/10	18.5 ± 0.2	30.9 ± 0.8	+12.4 ± 0.8	97.2	8.8	8.2
1,200	10/10	18.7 ± 0.4	28.2 ± 0.5	+9.5 ± 0.3	88.7	7.7	9.9

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 22
(f) One animal died at the end of the studies as a result of blood being taken.

TABLE 20. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE SIX-MONTH FEED STUDIES OF PURE PENTACHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 8	Week 24
MALE							
0	10/10	26.8 ± 0.4	39.3 ± 1.1	+12.5 ± 1.1		6.9	8.4
200	(e) 8/10	26.8 ± 0.6	38.9 ± 1.0	+12.8 ± 1.3	99.0	21.2	18.6
500	10/10	28.6 ± 0.6	40.5 ± 1.0	+11.9 ± 1.0	103.1	16.3	15.6
1,500	10/10	27.5 ± 0.5	36.3 ± 0.6	+8.8 ± 0.6	92.4	6.9	8.1
FEMALE							
0	10/10	19.3 ± 0.3	31.8 ± 0.7	+12.5 ± 0.7		8.9	9.6
200	10/10	19.4 ± 0.3	33.1 ± 1.1	+13.7 ± 1.0	104.1	8.1	8.8
500	10/10	19.4 ± 0.5	31.2 ± 0.9	+11.8 ± 0.5	98.1	9.0	8.5
1,500	10/10	18.5 ± 0.2	28.8 ± 0.4	+10.3 ± 0.3	90.6	9.0	8.6

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day (not corrected for scatter); animals were housed in varying numbers per cage with some cages, particularly those with a single occupant, having a high degree of feed wastage.
(e) Week of death: 16,17

No compound-related clinical signs were observed in mice fed 200 or 600 ppm of any of the four grades of pentachlorophenol or in mice fed 1,200 ppm EC-7 or 1,500 ppm pure pentachlorophenol. Mice that received 1,800 ppm technical-grade pentachlorophenol and two nonsurviving mice that received 1,200 ppm DP-2 displayed piloerection, enophthalmos, and hunched posture and appeared thin, weak, and inactive for several days before they died. No

compound-related effects on feed consumption were observed. The estimated amounts of impurities consumed are shown in Table 21.

Rectal body temperatures were recorded during exposure weeks 9 and 26 (Appendix I). No chemical-related effects were observed. In general, however, the body temperature of females was approximately 1° C higher than that in males (Table I11).

Neurobehavioral studies were conducted during exposure weeks 5 and 26 (data available at the NTP). No chemical-related neurobehavioral effects were observed at 5 weeks except for animals administered technical-grade pentachlorophenol, which showed a dose-dependent decrease in motor activity and rotarod performance. In contrast, exposure to each of the four grades of pentachlorophenol caused dose-related increases in both motor activity and startle response in female mice after 26 weeks' exposure. Only technical-grade pentachlorophenol caused this effect in male mice. There was no consistent chemical-related effect on pinna, corneal or righting reflexes, visual placement, grip strength, or rotarod testing.

One of the characteristic effects of the CDDs and CDFs is the induction of a cytochrome P450-mediated enzyme, AHH (Carlson et al., 1980). This effect is mediated by the *Ah* receptor. The ability of the four grades of pentachlorophenol to induce this enzyme was compared in these studies in order to indirectly assess the occupation of the *Ah* receptor by CDDs. Technical-grade pentachlorophenol induced AHH to a much greater extent than did pure pentachlorophenol (Table I1). Maximum induction was seen at the mid dose (600 ppm) of technical-grade pentachlorophenol. The intermediate degree of induction of AHH by DP-2 is consistent with its CDD and CDF content. Somewhat surprisingly, the highest dose of pure pentachlorophenol and EC-7 also induced AHH, although to a lesser degree than did technical-grade pentachlorophenol. The induction observed with the high dose of pure pentachlorophenol (1,500 ppm) and EC-7 (1,200 ppm) was comparable to the effect of DP-2 at 200 ppm. At this dose, female mice fed DP-2 consumed approximately 0.02, 1.0, and 6.3 µg/kg per day of the hexa-, hepta-, and octachlorodibenzodioxins and 0.5, 6.2, and 11.6 µg/kg per day of the hexa-, hepta-, and octachlorodibenzofurans (Table 21). In contrast, female mice fed 1,200 ppm EC-7 consumed approximately 0.04 µg/kg per day hexachlorodibenzodioxins, 0.12 µg/kg per day heptachlorodibenzodioxins, and 0.15 µg/kg per day octachlorodibenzodioxins. Female mice fed 1,500 ppm pure pentachlorophenol consumed no detectable level of the chlorinated dibenzodioxins but consumed from 27 to 600 µg/kg per day hepta-, octa-, and nonachlorohydroxydiphenyl ethers and hexa- and heptachlorohydroxydibenzofurans. Some induction of AHH activity has been previously noted after administration of relatively high doses (10 µmol/kg per day or approximately 4,400 µg/kg per day) for 3 days of certain halogenated diphenyl ethers to rats (Carlson et al., 1980). Therefore, the small induction of AHH by EC-7 and pure pentachlorophenol might conceivably be due to residual dibenzodioxin content or, in the case of pure pentachlorophenol, contamination with halogenated hydroxydiphenyl ethers or hydroxydibenzofurans. However, in view of the diverse CDD content of DP-2, EC-7, and pure pentachlorophenol, it seems equally likely that the small induction produced by EC-7 and pure pentachlorophenol is due to pentachlorophenol itself.

For assessment of the hepatic effects of any dibenzodioxin or dibenzofuran content of pentachlorophenol, it is important to note that the effects of pure pentachlorophenol were similar to those of EC-7 at all doses. Secondly, a tenfold lower dose of DP-2 was required to induce AHH than either pure pentachlorophenol or EC-7. Since maximum induction of AHH was noted with the lowest dose of technical-grade pentachlorophenol, one must conclude that the minimum effective dose required to produce this hepatic response differs by more than tenfold from that of pure pentachlorophenol or EC-7.

Surprisingly, there was no evidence for hepatic porphyria in female mice fed any of the grades of pentachlorophenol. A slight increase in hepatic porphyrin content was seen in mice fed 1,500 ppm pure pentachlorophenol, 200-1,200 ppm EC-7, 200-1,200 ppm DP-2, and 600 ppm

TABLE 21. EXPOSURE OF MICE TO VARIOUS IMPURITIES IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Impurity	Total Dose (µg)			Dose (µg/kg per day)		
	200 mg/kg	600 mg/kg	1,800 mg/kg	200 mg/kg	600 mg/kg	1,800 mg/kg
Technical Grade						
MALE						
Dichlorophenol	(b) --	--	--	--	--	--
Trichlorophenol	15.3	45.9	137	2.8	8.5	25.6
Tetrachlorophenol	5.8 mg	17.4 mg	52.8 mg	(c) 1.1 mg	3.2 mg	9.8 mg
Hexachlorobenzene	7.6	22.9	69.2	1.4	4.3	12.9
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	1.5	4.6	13.6	0.3	0.8	2.6
Heptachlorodibenzodioxin	45.3	136	408	8.4	25.3	75.9
Octachlorodibenzodioxin	218	637	1.9 mg	40.7	119	356
Pentachlorodibenzofuran	0.2	0.7	1.9	0.04	0.14	0.36
Hexachlorodibenzofuran	1.5	4.6	13.6	0.3	0.8	2.5
Heptachlorodibenzofuran	12.7	40.0	122	2.4	7.5	22.7
Octachlorodibenzofuran	6.55	20.0	59.2	1.2	3.7	11.0
Heptachlorohydroxydiphenyl ether	167	510	1.8 mg	31.2	94.9	339
Octachlorohydroxydiphenyl ether	3.6 mg	9.1 mg	25.5 mg	678	1.7 mg	4.7 mg
Nonachlorohydroxydiphenyl ether	5.5 mg	16.4 mg	49.1 mg	1.0 mg	3.1 mg	9.2 mg
Hexachlorohydroxydibenzofuran	237	728	1.8 mg	44.1	136	339
Heptachlorohydroxydibenzofuran	710	1.8 mg	7.3 mg	132	339	1.4 mg
FEMALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	15.9	47.6	143	3.6	10.9	32.7
Tetrachlorophenol	6.0 mg	18.1 mg	54.8 mg	1.4 mg	4.1 mg	12.6 mg
Hexachlorobenzene	7.9	23.8	71.8	1.8	5.5	16.5
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	1.6	4.8	14.3	0.4	1.1	3.3
Heptachlorodibenzodioxin	47.1	141	423	10.8	32.3	97.0
Octachlorodibenzodioxin	227	661	2.0 mg	51.9	152	455
Pentachlorodibenzofuran	0.2	0.8	2.0	0.05	0.17	0.46
Hexachlorodibenzofuran	1.5	4.6	14.2	0.3	1.1	3.2
Heptachlorodibenzofuran	13.2	41.6	127	3.0	9.5	29.0
Octachlorodibenzofuran	6.8	20.8	61.4	1.6	4.8	14.1
Heptachlorohydroxydiphenyl ether	174	529	1.9 mg	39.8	121	433
Octachlorohydroxydiphenyl ether	3.8 mg	9.5 mg	26.5 mg	866	2.2 mg	6.1 mg
Nonachlorohydroxydiphenyl ether	5.7 mg	17.0 mg	51.0 mg	1.3 mg	3.9 mg	11.7 mg
Hexachlorohydroxydibenzofuran	246	756	1.9 mg	56.3	173	433
Heptachlorohydroxydibenzofuran	737	1.9 mg	7.6 mg	169	433	1.7 mg

TABLE 21. EXPOSURE OF MICE TO VARIOUS IMPURITIES IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Impurity	Total Dose (μg)			Dose (μg/kg per day)		
	200 mg/kg	600 mg/kg	1,200 mg/kg	200 mg/kg	600 mg/kg	1,200 mg/kg
DP-2						
MALE						
Dichlorophenol	20	60	119	3.7	11	22
Trichlorophenol	67	202	404	13	38	75
Tetrachlorophenol	10.7 mg	32.1 mg	64.2 mg	2.0 mg	6.0 mg	12.0 mg
Hexachlorobenzene	2.3	6.9	13.8	0.4	1.3	2.6
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.09	0.27	0.54	0.02	0.05	0.10
Heptachlorodibenzodioxin	4.3	12.8	25.7	0.8	2.4	4.8
Octachlorodibenzodioxin	26.4	79.4	158	4.9	14.8	29.6
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	2.0	6.0	11.9	0.4	1.1	2.2
Heptachlorodibenzofuran	26.2	78.8	158	4.9	14.7	29.4
Octachlorodibenzofuran	49.0	147	293	9.1	27.3	54.6
Heptachlorohydroxydiphenyl ether	76.4	229	459	14.2	42.7	85.4
Octachlorohydroxydiphenyl ether	2.2 mg	6.5 mg	12.9 mg	400	1.2 mg	2.4 mg
Nonachlorohydroxydiphenyl ether	3.4 mg	10.1 mg	20.3 mg	629	1.9 mg	3.8 mg
Hexachlorohydroxydibenzofuran	107	321	642	20	60	120
Heptachlorohydroxydibenzofuran	473	1.4 mg	2.8 mg	88.1	265	529
FEMALE						
Dichlorophenol	21	62	124	4.7	14	28
Trichlorophenol	70	209	420	16	48	96
Tetrachlorophenol	11.1 mg	33.3 mg	66.7 mg	2.5 mg	7.6 mg	15.3 mg
Hexachlorobenzene	2.4	7.1	14.3	0.5	1.6	3.3
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.09	0.28	0.56	0.02	0.06	0.13
Heptachlorodibenzodioxin	4.4	13.3	26.7	1.0	3.0	6.1
Octachlorodibenzodioxin	27.4	82.4	165	6.3	18.9	37.7
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	2.1	6.2	12.4	0.5	1.4	2.8
Heptachlorodibenzofuran	27.2	81.8	164	6.2	18.7	37.5
Octachlorodibenzofuran	50.8	152	304	11.6	34.9	69.7
Heptachlorohydroxydiphenyl ether	79.4	238	476	18.2	54.5	109
Octachlorohydroxydiphenyl ether	2.2 mg	6.7 mg	13.4 mg	500	1.5 mg	3.1 mg
Nonachlorohydroxydiphenyl ether	3.5 mg	10.5 mg	21.1 mg	803	2.4 mg	4.8 mg
Hexachlorohydroxydibenzofuran	111	333	667	25	76	153
Heptachlorohydroxydibenzofuran	491	1.5 mg	3.0 mg	113	338	676

TABLE 21. EXPOSURE OF MICE TO VARIOUS IMPURITES IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Impurity	Total Dose (μg)			Dose (μg/kg per day)		
	200 mg/kg	600 mg/kg	1,200 mg/kg	200 mg/kg	600 mg/kg	1,200 mg/kg
Dowicide EC-7						
MALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	10.7	32	64	2.0	6.0	11.9
Tetrachlorophenol	14.4 mg	43 mg	86 mg	2.7 mg	8.0 mg	16.1 mg
Hexachlorobenzene	10	30	60	1.9	5.6	11.1
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.03	0.09	0.17	0.005	0.02	0.03
Heptachlorodibenzodioxin	0.08	0.24	0.49	0.02	0.05	0.09
Octachlorodibenzodioxin	0.11	0.32	0.63	0.02	0.06	0.12
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	0.02	0.06	0.12	0.004	0.01	0.02
Heptachlorodibenzofuran	0.02	0.07	0.14	0.004	0.01	0.03
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	--	--	--	--	--	--
Octachlorohydroxydiphenyl ether	--	--	--	--	--	--
Nonachlorohydroxydiphenyl ether	--	--	--	--	--	--
Hexachlorohydroxydibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydibenzofuran	--	--	--	--	--	--
FEMALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	11.2	33.3	67	2.6	7.6	15.3
Tetrachlorophenol	14.9 mg	44.8 mg	89 mg	3.4 mg	10.3 mg	20.5 mg
Hexachlorobenzene	10	31	62	2.4	7.1	14.2
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.03	0.09	0.18	0.007	0.02	0.04
Heptachlorodibenzodioxin	0.08	0.25	0.50	0.02	0.06	0.12
Octachlorodibenzodioxin	0.11	0.33	0.66	0.03	0.08	0.15
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	0.02	0.06	0.12	0.005	0.01	0.03
Heptachlorodibenzofuran	0.02	0.07	0.14	0.005	0.02	0.03
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	--	--	--	--	--	--
Octachlorohydroxydiphenyl ether	--	--	--	--	--	--
Nonachlorohydroxydiphenyl ether	--	--	--	--	--	--
Hexachlorohydroxydibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydibenzofuran	--	--	--	--	--	--

TABLE 21. EXPOSURE OF MICE TO VARIOUS IMPURITIES IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Impurity	Total Dose (μg)			Dose (μg/kg per day)		
	200 mg/kg	500 mg/kg	1,500 mg/kg	200 mg/kg	500 mg/kg	1,500 mg/kg
Pure Pentachlorophenol						
MALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	--	--	--	--	--	--
Tetrachlorophenol	2.1 mg	5.4 mg	16.1 mg	399	1.0 mg	3.0 mg
Hexachlorobenzene	1.5	3.8	11.5	0.28	0.71	2.1
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	--	--	--	--	--	--
Heptachlorodibenzodioxin	--	--	--	--	--	--
Octachlorodibenzodioxin	--	--	--	--	--	--
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	--	--	--	--	--	--
Heptachlorodibenzofuran	--	--	--	--	--	--
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	15	38	115	2.8	7.1	21
Octachlorohydroxydiphenyl ether	138	344	1.0 mg	25.6	64.1	192
Nonachlorohydroxydiphenyl ether	321	803	2.4 mg	59.8	149	448
Hexachlorohydroxydibenzofuran	168	420	1.3 mg	31.3	78.3	235
Heptachlorohydroxydibenzofuran	336	841	2.5 mg	62.6	157	470
FEMALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	--	--	--	--	--	--
Tetrachlorophenol	2.2 mg	5.6 mg	16.7 mg	509	1.3 mg	3.8 mg
Hexachlorobenzene	1.6	4.0	11.9	0.36	0.91	2.7
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	--	--	--	--	--	--
Heptachlorodibenzodioxin	--	--	--	--	--	--
Octachlorodibenzodioxin	--	--	--	--	--	--
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	--	--	--	--	--	--
Heptachlorodibenzofuran	--	--	--	--	--	--
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	16	40	119	3.6	9.1	27
Octachlorohydroxydiphenyl ether	143	357	1.1 mg	32.7	81.8	245
Nonachlorohydroxydiphenyl ether	333	833	2.5 mg	76.4	191	573
Hexachlorohydroxydibenzofuran	175	437	1.3 mg	40.0	100	300
Heptachlorohydroxydibenzofuran	349	873	2.6 mg	80	200	600

(a) These data were calculated based on estimated feed consumption of 4.2 g per day and mean body weights of 29.5 g for males and 23.1 g for females.
(b) -- = not present at detection limit
(c) mg = mg/kg per day

technical-grade pentachlorophenol. However, these minimal increases are not considered indicative of porphyria. Moreover, only very minimal increases in urinary uroporphyrins were observed in these studies, and the increases were statistically significant in animals fed pure pentachlorophenol but not in mice fed technical-grade pentachlorophenol.

Compound-related liver lesions consisting of karyomegaly, cytomegaly, and hepatocellular degeneration and necrosis were observed in mice administered any of the four grades of pentachlorophenol (Table 22). The liver lesions were less severe in females than in males for all four grades of pentachlorophenol.

The epithelial cells of the urinary bladder contained granular eosinophilic pigment without inflammation in all dosed groups of mice. The urinary bladder lesions were of minimal severity and were even less severe in females than in males that received EC-7 or pure pentachlorophenol. Nasal mucosal metaplasia was also compound related in mice that received EC-7 or pure pentachlorophenol. Examination of the liver and kidney by ultraviolet light did not reveal the presence of porphyria.

Additional compound-related lesions were observed mainly in animals that died before the end of the studies and included intrahepatic bile duct hyperplasia and inflammation (primarily in animals receiving the technical grade), epithelial hyperplasia of the gallbladder and degenerative changes in the bone marrow, spleen, thymus, and testis.

In the 6-month studies, absolute liver weights were significantly increased for all groups of dosed female mice, for all groups of male mice that received pure pentachlorophenol or technical-grade pentachlorophenol, for all but the low dose male mice that received 200 ppm DP-2, and for the high dose male group that received 1,200 ppm EC-7 (Tables I2 and I3). The relative liver weights were significantly increased for all groups of dosed female mice, for male mice that received technical-grade pentachlorophenol, and for mid and high dose groups of male mice that received 500 or 1,500 ppm pure pentachlorophenol, 600 or 1,200 ppm EC-7, or 600 or 1,200 ppm DP-2 (Tables I4 and I5).

Absolute spleen weights were significantly increased for all groups of dosed male mice except for the low dose groups that received 200 ppm technical-grade pentachlorophenol, DP-2, or pure pentachlorophenol (Tables I2 and I3). Absolute spleen weights were significantly decreased for female mice that received 600 ppm DP-2 and for all high dose groups of female mice except for the group that received 1,500 ppm pure pentachlorophenol. The relative spleen weights were significantly increased for all groups of male mice that received 200 ppm EC-7 or 500 ppm or more of a pentachlorophenol formulation. The relative spleen weights were significantly decreased for mid and high dose female mice that received 600 or 1,200 ppm DP-2.

A complete blood count (erythrocyte, leukocyte, and differential), hematocrit (packed cell volume), hemoglobin levels, and platelet and reticulocyte counts were measured in all mice at the end of the 6-month exposure (data available at the NTP). In addition, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume were calculated by using the above indices. No biologically significant abnormalities were observed in any of the values after exposure to EC-7 or pure pentachlorophenol. However, there were marginal effects on erythrocytes with DP-2 and technical-grade pentachlorophenol, as evidenced by slight but inconsistent decreases in the hematocrit and erythrocyte counts and increases in mean corpuscular volume and reticulocyte counts.

The serum glutamic-pyruvic transaminase (alanine aminotransferase) activity was significantly increased for all groups of dosed mice except low dose male mice that received 200 ppm EC-7 or DP-2 (Tables I8 and I9). The serum glutamic-oxaloacetic transaminase (aspartate aminotransferase) activity was significantly increased for high dose mice that received 600 ppm technical-grade pentachlorophenol or 1,200 ppm DP-2 and for high dose female mice that received 1,500 ppm pure pentachlorophenol. The γ-glutamyl transpeptidase activity was significantly increased for high dose male mice that received 1,500 ppm pure pentachlorophenol and for mid and high dose male mice that received 600 or

TABLE 22. NUMBERS OF MICE WITH SELECTED LESIONS IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Grade/ Concentration (ppm)	Liver						Urinary Bladder	Nasal Mucosa
	Hepato-cytomegaly	Inflammation	Pigmentation	Bile Duct Hyperplasia	Necrosis	Nuclear/ Alteration	Pigmentation	Metaplasia/ Goblet Cell Hyperplasia
MALE								
0	0	0	0	0	0	0	1	0
Technical Grade								
200	10	1	10	0	9	10	10	--
600	10	1	10	2	10	10	9	0
1,800	10	10	8	10	10	10	(b) 8	0
DP-2								
200	10	0	2	0	9	10	9	0
600	10	3	10	0	10	10	10	0
1,200	10	8	10	2	10	10	(b) 6	0
Dowicide EC-7								
200	10	0	2	0	9	10	8	0
600	10	1	6	0	8	10	8	(c) 5
1,200	10	2	8	1	10	10	10	(b) 8
Pure								
200	10	0	0	0	9	10	10	1
500	10	0	2	0	10	10	10	0
1,500	10	8	10	0	10	10	10	10
FEMALE								
0	0	0	0	0	0	0	0	3
Technical Grade								
200	10	0	9	0	8	10	(b) 8	0
600	10	1	9	0	9	10	6	0
1,800	10	10	10	10	10	10	(b) 9	0
DP-2								
200	10	0	2	0	2	7	5	--
600	10	0	10	0	10	10	10	0
1,200	10	2	10	0	10	10	(b) 9	2
Dowicide EC-7								
200	10	0	1	0	1	8	5	5
600	10	1	8	0	10	10	(b) 5	(b) 7
1,200	10	2	9	0	10	10	(b) 4	10
Pure								
200	10	0	0	0	6	8	(b) 3	7
500	10	0	3	0	10	10	4	(b) 6
1,500	10	0	10	0	10	10	(b) 9	10

(a) Ten animals were examined unless otherwise specified; common control groups used for all four grades of pentachlorophenol.
(b) Nine animals were examined.
(c) Seven animals were examined.

1,200 ppm DP-2. Data for γ-glutamyl transpeptidase activity were not reported for female mice.

Urine samples were collected at the end of the 6-month exposure period and were evaluated for specific gravity, color, and levels of creatinine (data available at the NTP). No consistent effects on specific gravity were seen in either sex. The color of the urine was darker than normal in males in the high dose groups exposed to each of the four grades of pentachlorophenol and in the high dose female mice exposed to EC-7 or pure pentachlorophenol. Urine creatinine levels were increased in the high dose males exposed to each of the four grades of pentachlorophenol but not in female mice.

The effects of pentachlorophenol exposure on immune function were determined by quantitating the plaque-forming cell (PFC) response following immunization with sheep erythrocytes and by measuring hemagglutination (HA) titers. The PFC response was markedly inhibited in mice exposed to technical-grade pentachlorophenol or the positive control, hydrocortisone acetate (Table I10), and to a lesser degree in mice exposed to DP-2 (high dose only). The antibody PFC response was not suppressed in mice administered Dowicide EC-7 or pure pentachlorophenol. The HA titers showed a similar trend but, in general, were much less consistent, probably reflecting the lack of sensitivity of this assay.

Dose Selection Rationale: Based primarily on the severity of the liver lesions, dietary concentrations selected for the 2-year studies of pentachlorophenol were 100 or 200 ppm for technical-grade pentachlorophenol and 100, 200, or 600 ppm for EC-7. DP-2 and pure pentachlorophenol were not selected for long-term study because of economic considerations and because the level of impurities in DP-2 was between that in EC-7 and in technical-grade pentachlorophenol. In addition, the degree of toxicity of EC-7 and pure pentachlorophenol was similar in the 6-month studies. At that time, EC-7 also was considered a commercially viable alternative to technical-grade pentachlorophenol. Finally, the pure pentachlorophenol available contained chlorinated hydroxydiphenyl ethers and hydroxydibenzofurans at fairly high levels which were considered to be potentially toxic in 2-year studies.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Both grades of pentachlorophenol (technical grade and EC-7) used in the 2-year studies were approximately 90% pure. The level of exposure to the impurities is shown in Table 23.

Technical-Grade Pentachlorophenol: Mean body weights of dosed and control male mice were comparable throughout most of the study even though the weights of the groups exposed to pentachlorophenol were slightly higher at the start of the study (Table 24 and Figure 9). Mean body weights of high dose female mice were 5%-13% lower than those of controls after week 82. The average daily feed consumption by all groups of dosed mice was 97% that by controls (Tables F1 and F2). The average amount of technical-grade pentachlorophenol consumed per day was approximately 18 or 35 mg/kg for low dose or high dose male mice and 17 or 35 mg/kg for low dose or high dose female mice. No compound-related clinical signs were observed.

EC-7: Mean body weights of high dose male mice were 4%-12% lower than those of controls from week 36 to week 89, after which they returned to control levels (Table 25 and Figure 10). Mean body weights of high dose female mice were 7%-15% lower than those of controls from week 40 to week 76 and then were 17%-22% lower. Mean body weights of mid dose female mice were 6%-12% lower than those of controls from week 80 to the end of the study. No compound-related clinical signs were observed. The average daily feed consumption by each dose group was within 10% of that by controls (Tables F3 and F4). The average amount of EC-7 consumed per day was approximately 18, 37, or 118 mg/kg for low dose, mid dose, or high dose male mice and 17, 34, or 114 mg/kg for low dose, mid dose, or high dose female mice.

TABLE 23. EXPOSURE OF MICE TO VARIOUS IMPURITIES IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (a)

Impurity	Total Dose (μg)		Dose (μg/kg per day)	
	100 mg/kg	200 mg/kg	100 mg/kg	200 mg/kg
Technical Grade				
MALE				
Dichlorophenol	(b) --	--	--	--
Trichlorophenol	31.0	62.0	1.1	2.3
Tetrachlorophenol	11.8 mg	23.6 mg	430	860
Hexachlorobenzene	15.9	31	0.6	1.1
Tetrachlorodibenzodioxin	--	--	--	--
Hexachlorodibenzodioxin	3.1	6.2	0.11	0.23
Heptachlorodibenzodioxin	91.6	184	3.3	6.7
Octachlorodibenzodioxin	430	865	15.6	31
Pentachlorodibenzofuran	0.43	0.87	0.016	0.03
Hexachlorodibenzofuran	3.1	6.5	0.11	0.24
Heptachlorodibenzofuran	30	50	1.0	2.0
Octachlorodibenzofuran	10	30	0.5	1.0
Heptachlorohydroxydiphenyl ether	340	680	10	20
Octachlorohydroxydiphenyl ether	5.9 mg	11.8 mg	220	430
Nonachlorohydroxydiphenyl ether	11.0 mg	22.1 mg	400	800
Hexachlorohydroxydibenzofuran	500	990	20	40
Heptachlorohydroxydibenzofuran	1.5 mg	2.9 mg	50	110
FEMALE				
Dichlorophenol	--	--	--	--
Trichlorophenol	28.1	56.2	1.1	2.2
Tetrachlorophenol	10.7 mg	21.4 mg	415	830
Hexachlorobenzene	14	28	0.54	1.1
Tetrachlorodibenzodioxin	--	--	--	--
Hexachlorodibenzodioxin	2.8	5.6	0.11	0.22
Heptachlorodibenzodioxin	82.9	167	3.2	6.5
Octachlorodibenzodioxin	390	780	15.1	31
Pentachlorodibenzofuran	0.36	0.79	0.014	0.03
Hexachlorodibenzofuran	2.8	5.8	0.11	0.22
Heptachlorodibenzofuran	20	50	1.0	1.9
Octachlorodibenzofuran	10	20	0.5	1.0
Heptachlorohydroxydiphenyl ether	310	620	10	20
Octachlorohydroxydiphenyl ether	5.4 mg	10.7 mg	210	420
Nonachlorohydroxydiphenyl ether	10.0 mg	20.0 mg	390	780
Hexachlorohydroxydibenzofuran	450	900	20	30
Heptachlorohydroxydibenzofuran	1.3 mg	2.6 mg	50	100

TABLE 23. EXPOSURE TO VARIOUS IMPURITIES OF MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (Continued)

Impurity	Total Dose (µg)			Dose (µg/kg per day)		
	100 mg/kg	200 mg/kg	600 mg/kg	100 mg/kg	200 mg/kg	600 mg/kg
Dowicide EC-7						
MALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	21.7	43.4	131	0.8	1.6	4.7
Tetrachlorophenol	29 mg	58 mg	175 mg	(c) 1.1 mg	2.1 mg	6.3 mg
Hexachlorobenzene	20.2	40.3	121	0.7	1.5	4.4
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.06	0 12	0.35	0.002	0.004	0.01
Heptachlorodibenzodioxin	0.16	0.33	0.99	0.006	0.01	0.04
Octachlorodibenzodioxin	0.21	0.43	1 3	0.008	0.02	0.05
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	0.04	0 08	0.24	0.001	0.003	0.009
Heptachlorodibenzofuran	0.05	0.09	0.28	0.002	0.003	0.01
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	--	--	--	--	--	--
Octachlorohydroxydiphenyl ether	--	--	--	--	--	--
Nonachlorohydroxydiphenyl ether	--	--	--	--	--	--
Hexachlorohydroxydibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydibenzofuran	--	--	--	--	--	--
FEMALE						
Dichlorophenol	--	--	--	--	--	--
Trichlorophenol	19.7	39.4	118	0.8	1.5	4.6
Tetrachlorophenol	26 mg	53 mg	159 mg	1.0 mg	2.0 mg	5.8 mg
Hexachlorobenzene	18.3	36.6	110	0.7	1.4	4.2
Tetrachlorodibenzodioxin	--	--	--	--	--	--
Hexachlorodibenzodioxin	0.05	0.11	0.32	0.002	0.004	0.01
Heptachlorodibenzodioxin	0.15	0.30	0.89	0.006	0.01	0.03
Octachlorodibenzodioxin	0.19	0.39	1.2	0.008	0.02	0.05
Pentachlorodibenzofuran	--	--	--	--	--	--
Hexachlorodibenzofuran	0.04	0 07	0.22	0.001	0.003	0.008
Heptachlorodibenzofuran	0.04	0 08	0.25	0.002	0.003	0.01
Octachlorodibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydiphenyl ether	--	--	--	--	--	--
Octachlorohydroxydiphenyl ether	--	--	--	--	--	--
Nonachlorohydroxydiphenyl ether	--	--	--	--	--	--
Hexachlorohydroxydibenzofuran	--	--	--	--	--	--
Heptachlorohydroxydibenzofuran	-	-	--	--	-	--

(a) These data were calculated based on feed consumption of 4.3 g per day for males and 3.9 g per day for females and on mean body weights of 38.2 g for males and 35.8 g for females.
(b) -- = not present at detection limit
(c) mg = mg/kg per day

TABLE 24. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL

Weeks on Study	Control		100 ppm			200 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	24 6	35	25 7	104	50	25 6	104	50
1	26 7	35	26 4	99	50	26 8	100	50
3	29 0	35	28 7	99	50	29 2	101	50
4	29 7	35	29 5	99	50	29 9	101	50
5	30 3	35	30 0	99	50	30 9	102	50
6	31 5	35	31 5	100	50	32 5	103	50
7	31 5	35	32 1	102	50	33 0	105	50
8	32 1	35	32 0	100	50	32 8	102	50
9	32 4	35	32 2	99	50	31 6	98	50
10	32 7	35	33 0	101	50	32 5	99	50
11	32 5	35	33 3	102	50	33 4	103	50
12	32 2	35	33 7	105	50	34 3	107	50
16	35 2	34	35 2	100	50	35 8	102	50
20	36 5	33	36.3	99	50	37 2	102	49
25	35 4	33	37 3	105	50	37 2	105	49
30	37 2	32	38 1	102	49	38 3	103	49
34	38 2	32	39 2	103	49	39 5	103	49
38	38 7	31	40 1	104	49	39 9	103	49
42	39 7	30	39 9	101	49	39 7	100	49
46	40 1	30	40 2	100	48	41 2	103	48
50	39 9	28	40 3	101	45	41 2	103	48
57	39 9	27	40 6	102	45	40 6	102	44
61	37 2	23	40 1	108	44	39 6	106	44
66	38 0	23	40 3	106	44	40 0	105	43
70	37 6	23	38 1	101	43	41 6	111	41
74	40 2	20	42 7	106	42	42 0	104	40
78	37 6	18	37 7	100	39	37 0	98	38
82	37 2	17	38 6	104	38	37 8	102	36
87	37 3	15	37 7	101	36	38 1	102	32
91	37 1	15	37 3	101	32	39 2	106	30
95	37 3	15	37 0	99	30	38 3	103	26
100	36 8	12	36 7	100	27	38 0	103	23
103	37 2	12	36 8	99	24	38 3	103	22
FEMALE								
0	20 3	35	18 2	90	50	19 9	98	50
1	20 9	35	20 5	98	50	20 3	97	50
3	22 4	35	21 9	98	50	22 3	100	50
4	22 7	35	22 6	100	50	22 8	100	50
5	23 3	35	22 9	98	50	23 1	99	50
6	23 9	35	24 1	101	50	23 1	97	50
7	24 5	35	24 5	100	50	25 0	102	50
8	25 1	35	24 6	98	50	25 1	100	50
9	24 9	35	25 3	102	50	25 4	102	50
10	25 4	35	25 5	100	50	25 4	100	50
11	25 7	35	25 3	98	50	25 0	97	50
12	25 8	35	25 9	100	50	25 6	99	50
16	27 2	35	27 2	100	50	26 8	99	50
20	28 3	35	29 2	103	50	28 9	102	50
25	29 6	34	30 2	102	50	29 0	98	50
30	31 4	33	31 7	101	50	31 0	99	50
34	33 2	33	32 5	98	50	32 2	97	49
38	33 3	33	34 0	102	50	32 8	98	49
42	35 7	33	35 4	99	50	34 4	96	49
46	37 0	33	36 3	98	50	36 2	98	49
50	36 6	33	37 6	103	50	34 3	94	49
57	37 6	33	38 3	102	49	36 3	97	48
61	37 7	33	38 7	103	48	37 1	98	47
66	40 1	33	38 8	97	47	37 2	93	46
70	39 6	33	39 9	101	46	38 2	96	46
74	41 0	33	40 6	99	46	39 7	97	45
78	40 0	33	40 9	102	46	39 2	98	45
82	41 9	33	42 5	101	46	39 6	95	44
87	41 3	32	41 7	101	46	38 6	93	44
91	41 8	30	42 3	101	46	38 4	92	42
95	42 4	30	41 5	98	46	37 0	87	40
100	42 5	29	43 7	103	43	39 0	92	34
103	41 8	29	43 6	104	41	38 4	92	32

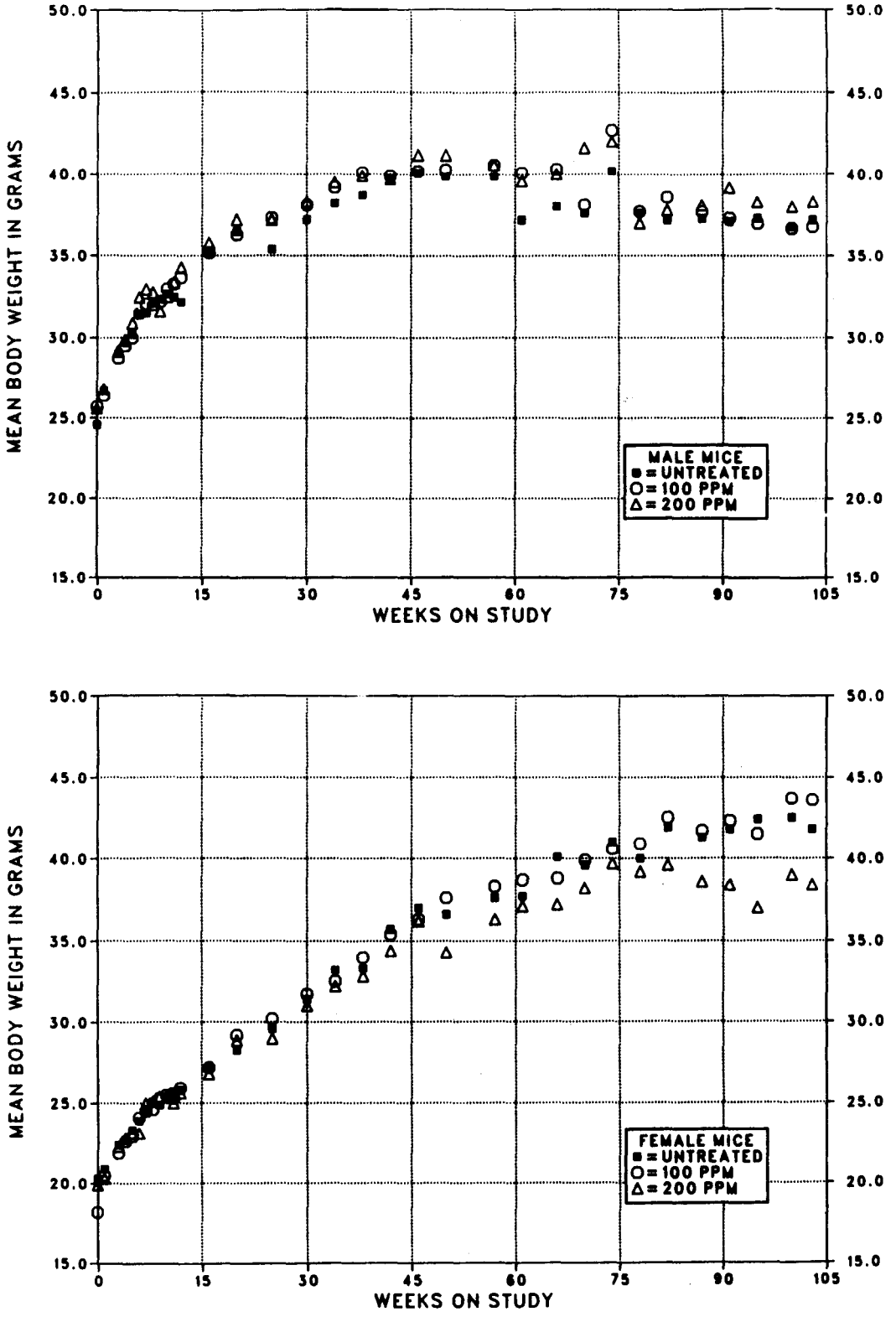


FIGURE 9. GROWTH CURVES FOR MICE FED DIETS CONTAINING TECHNICAL-GRADE PENTACHLOROPHENOL FOR TWO YEARS

TABLE 25. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL, DOWICIDE EC-7

Weeks on Study	Control		100 ppm			200 ppm			600 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE											
0	23.7	35	23.3	98	50	23.5	99	50	23.5	99	50
1	25.3	35	25.0	99	50	25.3	100	50	25.0	99	50
2	26.2	35	26.3	100	50	26.4	101	50	26.1	100	50
3	27.7	35	27.6	100	50	27.1	98	50	27.2	98	50
4	28.9	35	28.6	99	50	28.3	98	49	28.2	98	50
5	29.1	35	28.8	99	50	29.3	101	49	28.6	98	50
6	29.7	35	29.5	99	50	29.6	100	49	29.2	98	50
7	30.4	35	30.1	99	50	30.1	99	49	29.9	98	50
8	31.2	35	30.7	98	50	31.1	100	49	31.1	100	50
9	31.6	35	30.9	98	50	30.9	98	49	30.0	95	49
10	32.5	35	32.0	98	49	32.0	98	49	31.7	98	49
11	32.3	35	31.8	98	49	32.2	100	49	31.6	98	49
12	32.9	35	32.6	99	49	32.9	100	49	32.6	99	49
13	32.8	35	33.5	102	49	33.9	103	49	33.1	101	49
18	35.5	35	35.0	99	49	35.2	99	49	34.5	97	49
22	36.1	35	36.0	100	49	35.6	99	47	35.5	98	49
28	37.2	35	36.2	97	49	36.8	99	47	36.4	98	49
32	38.2	33	36.5	96	49	37.7	99	47	37.2	97	49
36	38.1	33	37.4	98	48	38.2	100	47	36.6	96	48
40	39.1	33	39.1	100	48	39.0	100	47	36.6	94	48
45	39.3	33	38.6	98	47	38.6	98	42	36.6	93	48
49	38.1	33	35.5	93	47	37.6	99	41	36.3	95	48
53	39.5	33	37.3	94	47	37.4	95	39	36.6	93	47
57	39.9	33	38.4	96	47	37.5	94	39	37.3	93	46
60	39.6	33	38.0	96	47	37.6	95	38	36.4	92	46
65	37.1	33	38.2	103	45	37.7	102	38	32.8	88	46
71	38.9	29	37.4	96	43	37.4	96	38	37.2	96	45
76	38.2	28	35.6	93	41	36.4	95	38	36.0	94	45
80	37.8	28	35.8	95	41	36.2	96	36	35.7	94	44
84	37.8	28	36.5	97	40	37.2	98	35	35.1	93	44
89	39.3	28	35.0	89	37	35.3	90	32	36.7	93	40
93	36.4	28	35.5	98	37	36.2	99	32	35.8	98	39
97	36.4	27	33.8	93	34	34.7	95	30	34.9	96	38
101	36.2	26	35.5	98	30	35.0	97	29	35.3	98	37
103	36.9	25	34.5	93	29	34.7	94	29	35.8	97	35
FEMALE											
0	18.6	35	18.2	98	50	18.5	99	50	18.4	99	50
1	19.4	35	21.0	108	50	19.7	102	50	21.1	109	50
2	20.7	35	20.5	99	50	20.9	101	50	20.7	100	50
3	21.6	35	21.2	98	50	22.1	102	50	21.3	99	50
4	22.3	35	22.3	100	50	22.2	100	50	22.1	99	50
5	22.2	35	22.8	103	50	22.3	100	50	22.5	101	50
6	23.0	35	23.0	100	50	23.0	100	50	22.8	99	50
7	22.9	35	23.3	102	50	23.4	102	50	23.3	102	50
8	24.4	35	24.2	99	50	24.0	98	50	24.2	99	50
9	24.3	35	24.6	101	50	24.5	101	50	23.5	97	50
10	24.8	35	24.9	100	50	25.0	101	50	24.8	100	50
11	24.6	35	25.2	102	50	25.2	102	50	25.0	102	50
12	25.2	35	25.4	101	50	25.8	102	50	25.2	100	50
13	25.7	35	25.9	101	50	26.2	102	50	25.7	100	50
18	27.8	35	28.1	101	50	27.8	100	50	27.4	99	50
22	28.6	35	28.4	99	50	29.4	103	50	28.6	100	50
28	30.5	35	30.1	99	50	30.7	101	50	29.5	97	50
32	31.5	35	31.8	101	50	31.6	100	50	30.9	98	50
36	33.3	35	33.2	100	50	33.1	99	50	31.5	95	50
40	35.0	35	34.3	98	50	34.9	100	50	32.4	93	50
45	35.8	35	35.2	98	50	35.8	100	50	32.9	92	50
49	35.3	35	35.0	99	49	35.1	99	50	31.7	90	50
53	35.8	35	35.1	98	49	35.4	99	50	31.8	89	50
57	36.0	35	34.8	97	49	36.6	102	50	31.2	87	50
60	37.0	35	36.3	98	49	37.5	101	50	31.8	86	50
65	34.5	35	35.6	103	47	35.4	103	50	31.3	91	50
71	37.2	34	37.9	102	45	37.0	99	50	32.6	88	48
76	38.7	34	39.7	103	44	37.6	97	49	32.8	85	46
80	39.6	34	39.5	100	43	37.3	94	49	32.7	83	45
84	40.0	34	38.8	97	40	36.7	92	49	32.9	82	45
89	40.4	34	39.4	98	39	36.8	91	49	33.4	83	44
93	40.4	33	39.4	98	34	38.0	94	44	31.8	79	44
97	40.7	33	38.2	94	33	35.9	88	44	33.3	82	41
101	42.0	32	39.2	93	32	38.1	91	40	32.7	78	40
103	41.9	29	40.1	96	28	38.7	92	38	34.2	82	39

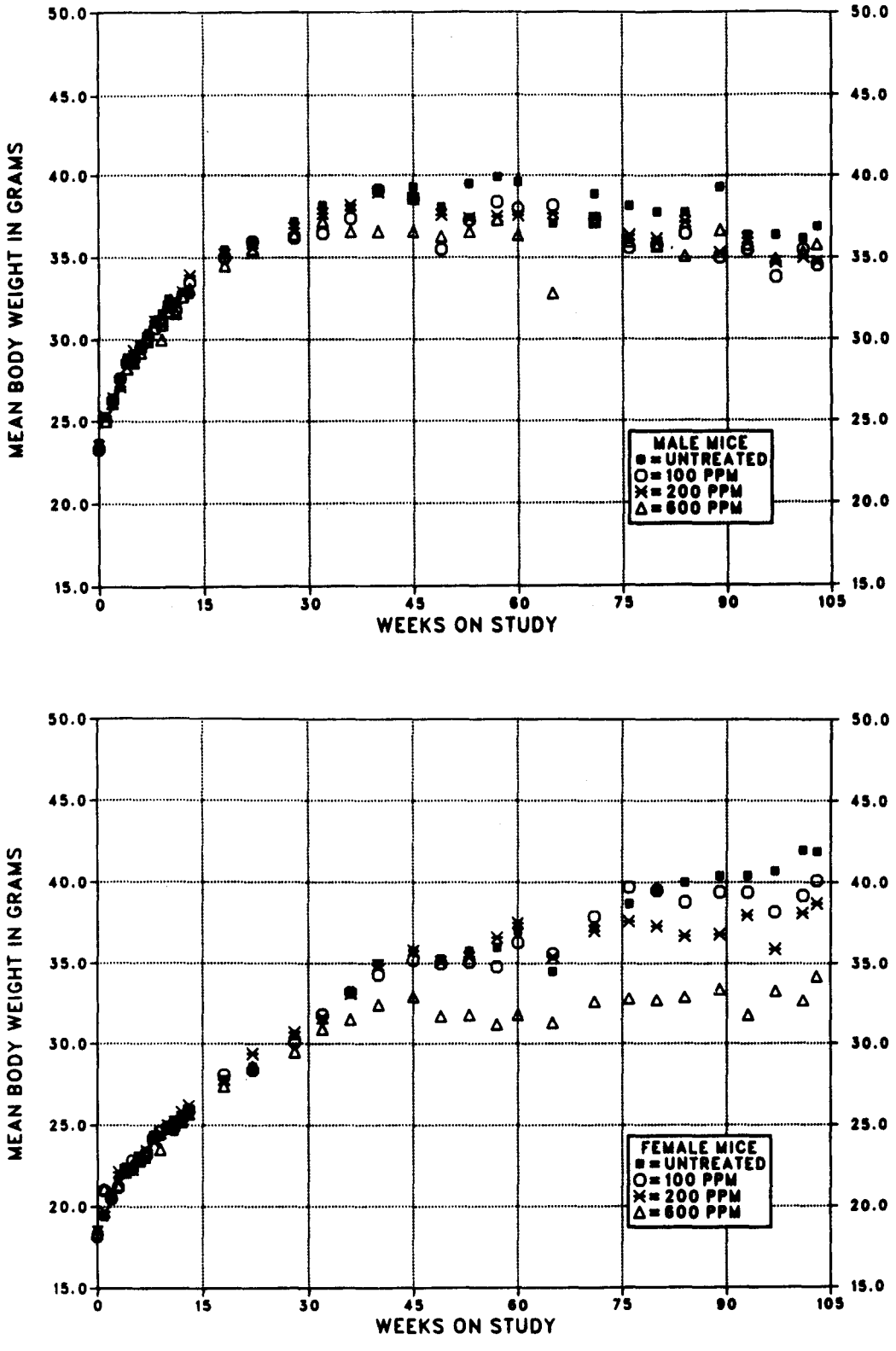


FIGURE 10. GROWTH CURVES FOR MICE FED DIETS CONTAINING PENTACHLOROPHENOL, DOWICIDE EC-7, FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing pentachlorophenol at the concentrations used in these studies and for controls are shown in Tables 26 and 27 and in the Kaplan and Meier curves in Figures 11 and 12. The survival of the low dose group of female mice that received EC-7 was significantly lower than that of controls after day 628. No other significant differences in survival were observed between any groups of either sex. It should be noted, however, that the survival of the male control group in the technical-grade pentachlorophenol study was abnormally low (34%) compared with that of the EC-7 control group (71%).

TABLE 26. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Control	100 ppm	200 ppm
MALE (a)			
Animals initially in study	35	50	50
Nonaccidental deaths before termination (b)	23	26	24
Accidentally killed	0	0	(c) 4
Killed at termination	12	24	22
Survival P values (d)	0.070	0.078	0.063
FEMALE (a)			
Animals initially in study	35	50	50
Nonaccidental deaths before termination (b)	6	9	18
Killed at termination	28	41	30
Died during the termination period	1	0	2
Survival P values (d)	0.055	0.821	0.122

(a) First day of terminal-kill period: 729
(b) Includes animals killed in a moribund condition
(c) Cage was flooded.
(d) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

TABLE 27. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Control	100 ppm	200 ppm	600 ppm
MALE (a)				
Animals initially in study	35	50	50	50
Nonaccidental deaths before termination (b)	10	22	21	15
Killed at termination	25	28	29	35
Survival P values (c)	0.496	0.255	0.241	0.899
FEMALE (a)				
Animals initially in study	35	50	50	50
Nonaccidental deaths before termination (b)	6	21	12	11
Accidentally killed	0	1	0	0
Killed at termination	29	28	38	39
Survival P values (c)	0.567	0.016	0.558	0.687

(a) First day of terminal-kill period: 727
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

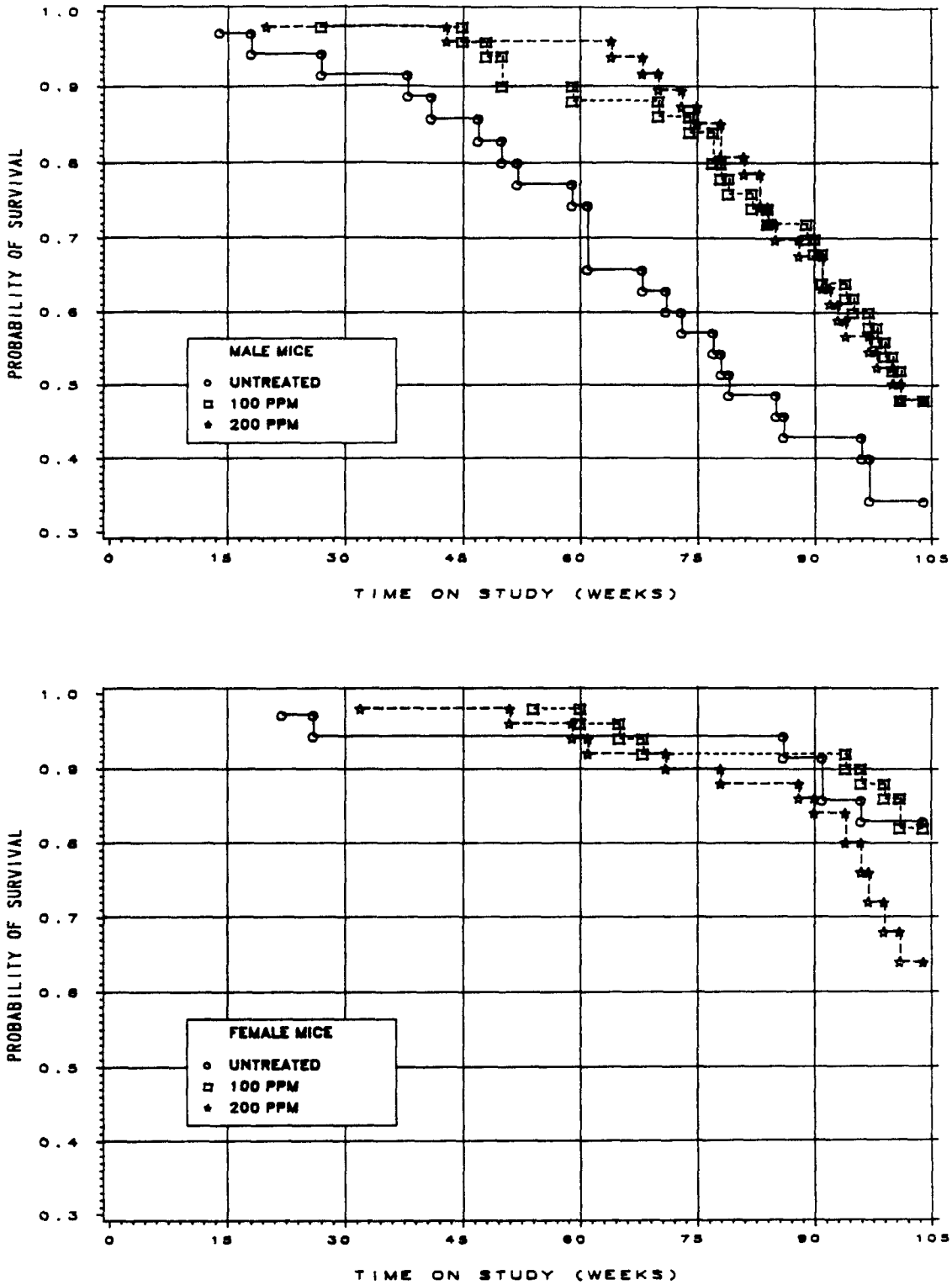


FIGURE 11. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING TECHNICAL-GRADE PENTACHLOROPHENOL FOR TWO YEARS

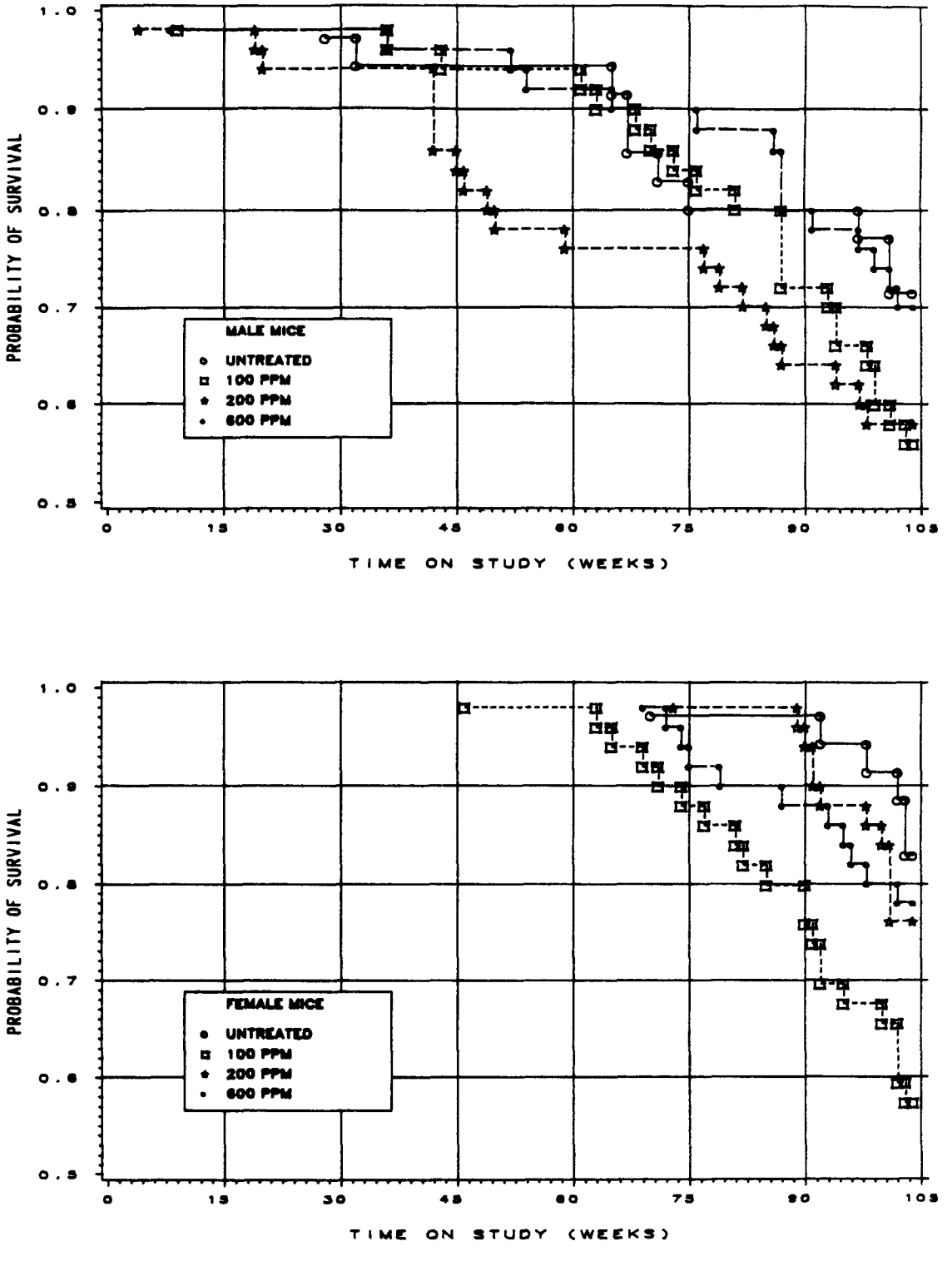


FIGURE 12. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING PENTACHLOROPHENOL, DOWICIDE EC-7, FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, adrenal gland, circulatory system, spleen, nose, and mammary gland.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female mice, respectively, receiving technical-grade pentachlorophenol.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively, receiving EC-7.

When survival differences were taken into account, there were no significant differences in tumor incidence between the technical-grade pentachlorophenol and Dowicide EC-7 control groups. As a supplemental procedure, analyses were performed to compare tumor incidences in dosed groups with those in combined control groups.

Liver

Nonneoplastic Effects: Technical-grade pentachlorophenol and Dowicide EC-7 caused a spectrum of nonneoplastic lesions in the liver of male and female mice (Table 28). There was diffuse enlargement of hepatocytes (cytomegaly), which were pleomorphic and often had vacuolated cytoplasm and vesicular nuclei with multiple nucleoli. Discrete foci of hepatocytes with finely vacuolated cytoplasm (clear cell focus) were present in some livers. There was widespread individual cell necrosis of hepatocytes with a diffuse, low-grade inflammatory infiltrate consisting of mononuclear cells and neutrophils in the sinusoids (chronic active inflammation). These changes were accompanied by an accumulation of yellow-brown pigment (lipofuscin and cellular debris) in Kupffer cells and proliferation of hematopoietic cells. An increase in small bile ductules (bile duct hyperplasia) with periportal fibrosis in dosed mice was also observed.

TABLE 28. NUMBERS OF MICE WITH LIVER LESIONS IN THE TWO-YEAR FEED STUDIES OF TECHNICAL-GRADE PENTACHLOROPHENOL AND PENTACHLOROPHENOL, DOWICIDE EC-7

Lesion	Technical Grade			Dowicide EC-7			
	Control	100 ppm	200 ppm	Control	100 ppm	200 ppm	600 ppm
MALE							
No. examined	32	47	48	35	48	48	49
Clear cell focus	0	11	6	0	19	21	19
Multifocal proliferation of hematopoietic cells	2	20	27	1	20	16	40
Diffuse chronic active inflammation	0	42	46	0	36	44	43
Multifocal pigmentation	0	45	46	0	40	37	45
Acute diffuse necrosis	0	41	45	0	47	47	46
Diffuse cytomegaly	0	47	48	0	48	48	47
Bile duct hyperplasia	0	22	37	1	3	5	32
Hepatocellular adenoma	5	20	33	5	13	17	32
Hepatocellular carcinoma	2	10	12	1	7	7	9
FEMALE							
No. examined	33	49	50	34	50	49	48
Clear cell focus	1	3	17	1	2	13	26
Multifocal proliferation of hematopoietic cells	14	8	33	20	37	35	45
Diffuse chronic active inflammation	0	34	44	0	4	29	47
Multifocal pigmentation	0	37	47	0	4	32	48
Acute diffuse necrosis	0	44	47	0	21	49	48
Diffuse cytomegaly	0	48	48	0	37	49	48
Bile duct hyperplasia	0	1	2	0	0	1	40
Hepatocellular adenoma	3	8	8	1	3	6	30
Hepatocellular carcinoma	0	1	1	0	1	0	2

The incidences of hepatocellular adenomas and hepatocellular carcinomas were significantly greater in male mice given 200 ppm or more technical-grade pentachlorophenol or EC-7 than in controls; the incidence of hepatocellular neoplasms increased markedly in female mice given 600 ppm EC-7 (Table 29).

The hepatocellular neoplasms in dosed mice given technical-grade pentachlorophenol or Dowicide EC-7 were similar in histologic appearance and had variable cell patterns ranging from very small hepatocytes with basophilic cytoplasm to large vacuolated cells similar to those seen in other areas of the liver. The adenomas were relatively discrete proliferative lesions that compressed the adjacent parenchyma, and there was loss of lobular architecture within the neoplasms. Hepatocellular carcinomas had more heterogeneous growth patterns and usually contained branching trabeculae of hepatocytes which were four to six cell layers thick. The cells were often pleomorphic and anaplastic.

TABLE 29. ANALYSIS OF HEPATOCELLULAR TUMORS IN MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (a)

	Control	100 ppm (b)	200 ppm (b)	600 ppm (b)
MALE				
TECHNICAL GRADE				
Adenoma				
Overall Rates	5/32 (16%)	20/47 (43%)	33/48 (69%)	
Adjusted Rates	27.6%	65.1%	88.5%	
Terminal Rates	2/12 (17%)	14/24 (58%)	18/22 (82%)	
Day of First Observation	330	413	376	
Life Table Tests	P<0.001	P=0.076	P<0.001	
Logistic Regression Tests	P<0.001	P=0.037	P<0.001	
Carcinoma				
Overall Rates	2/32 (6%)	10/47 (21%)	12/48 (25%)	
Adjusted Rates	11.4%	33.2%	39.5%	
Terminal Rates	0/12 (0%)	5/24 (21%)	6/22 (27%)	
Day of First Observation	498	521	512	
Life Table Tests	P=0.069	P=0.190	P=0.090	
Logistic Regression Tests	P=0.046	P=0.127	P=0.049	
Adenoma or Carcinoma (c)				
Overall Rates	7/32 (22%)	26/47 (55%)	37/48 (77%)	
Adjusted Rates	35.8%	75.7%	89.6%	
Terminal Rates	2/12 (17%)	16/24 (67%)	18/22 (82%)	
Day of First Observation	330	413	376	
Life Table Tests	P<0.001	P=0.069	P=0.002	
Logistic Regression Tests	P<0.001	P=0.015	P<0.001	
Life Table Tests (d)	P=0.001	P=0.008	P=0.001	
Logistic Regression Tests (d)	P=0.001	P=0.009	P<0.002	
DOWICIDE EC-7				
Adenoma				
Overall Rates	5/35 (14%)	13/48 (27%)	17/48 (35%)	32/49 (65%)
Adjusted Rates	20.0%	41.6%	53.0%	84.1%
Terminal Rates	5/25 (20%)	10/28 (36%)	14/29 (48%)	29/35 (83%)
Day of First Observation	727	613	608	536
Life Table Tests	P<0.001	P=0.057	P=0.008	P<0.001
Logistic Regression Tests	P<0.001	P=0.083	P=0.007	P<0.001
Carcinoma				
Overall Rates	1/35 (3%)	7/48 (15%)	7/48 (15%)	9/49 (18%)
Adjusted Rates	4.0%	20.2%	24.1%	25.0%
Terminal Rates	1/25 (4%)	2/28 (7%)	7/29 (24%)	8/35 (23%)
Day of First Observation	727	612	727	717
Life Table Tests	P=0.127	P=0.062	P=0.047	P=0.034
Logistic Regression Tests	P=0.108	P=0.075	P=0.045	P=0.032
Adenoma or Carcinoma (c)				
Overall Rates	6/35 (17%)	19/48 (40%)	21/48 (44%)	34/49 (69%)
Adjusted Rates	24.0%	53.8%	65.5%	87.1%
Terminal Rates	6/25 (24%)	12/28 (43%)	18/29 (62%)	30/35 (86%)
Day of First Observation	727	612	608	536
Life Table Tests	P<0.001	P=0.009	P=0.002	P<0.001
Logistic Regression Tests	P<0.001	P=0.015	P=0.001	P<0.001
Life Table Tests (d)	P<0.001	P=0.037	P=0.009	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.030	P<0.004	P<0.001

TABLE 29. ANALYSIS OF HEPATOCELLULAR TUMORS IN MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (Continued)

	Control	100 ppm	200 ppm	600 ppm
FEMALE				
TECHNICAL GRADE				
Adenoma				
Overall Rates	3/33 (9%)	8/49 (16%)	8/50 (16%)	
Adjusted Rates	10.7%	19.5%	24.0%	
Terminal Rates	3/28 (11%)	8/41 (20%)	7/32 (22%)	
Day of First Observation	729	729	682	
Life Table Tests	P=0.113	P=0.261	P=0.148	
Logistic Regression Tests	P=0.151	P=0.261	P=0.193	
Carcinoma				
Overall Rates	0/33 (0%)	1/49 (2%)	1/50 (2%)	
Adenoma or Carcinoma (e)				
Overall Rates	3/33 (9%)	9/49 (18%)	9/50 (18%)	
Adjusted Rates	10.7%	21.4%	25.9%	
Terminal Rates	3/28 (11%)	8/41 (20%)	7/32 (22%)	
Day of First Observation	729	707	673	
Life Table Tests	P=0.080	P=0.193	P=0.104	
Logistic Regression Tests	P=0.131	P=0.227	P=0.154	
Life Table Tests (d)	P=0.007	P=0.034	P=0.011	
Logistic Regression Tests (d)	P=0.014	P=0.036	P=0.020	
DOWICIDE EC-7				
Adenoma				
Overall Rates	1/34 (3%)	3/50 (6%)	6/49 (12%)	30/48 (63%)
Adjusted Rates	3.4%	10.7%	15.8%	75.0%
Terminal Rates	1/29 (3%)	3/28 (11%)	6/38 (16%)	29/39 (74%)
Day of First Observation	727	727	727	668
Life Table Tests	P<0.001	P=0.291	P=0.110	P<0.001
Logistic Regression Tests	P<0.001	P=0.291	P=0.110	P<0.001
Carcinoma				
Overall Rates	0/34 (0%)	1/50 (2%)	0/49 (0%)	2/48 (4%)
Adenoma or Carcinoma (e)				
Overall Rates	1/34 (3%)	4/50 (8%)	6/49 (12%)	31/48 (65%)
Adjusted Rates	3.4%	13.8%	15.8%	77.5%
Terminal Rates	1/29 (3%)	3/28 (11%)	6/38 (16%)	30/39 (77%)
Day of First Observation	727	720	727	668
Life Table Tests	P<0.001	P=0.168	P=0.110	P<0.001
Logistic Regression Tests	P<0.001	P=0.172	P=0.110	P<0.001
Life Table Tests (d)	P<0.001	P=0.250	P=0.154	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.319	P=0.154	P<0.001

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix F.
(c) Historical incidence at study laboratory (mean ± SD): 101/343 (29% ± 8%); historical incidence in NTP studies: 609/2,032 (30% ± 8%)
(d) P values vs. combined control groups for technical-grade pentachlorophenol and Dowicide EC-7
(e) Historical incidence at study laboratory (mean ± SD): 28/347 (8% ± 4%); historical incidence in NTP studies: 184/2,032 (9% ± 5%)

Adrenal Gland

Technical-Grade Pentachlorophenol--Medullary hyperplasia was observed at increased incidences in dosed male mice (Table 30). Pheochromocytomas in male (but not in female) mice occurred with a significant positive trend; the incidences in the dosed groups were significantly greater than that in controls. No significant increase in the incidence of malignant pheochromocytomas was observed. However, a large proportion of the pheochromocytomas were bilateral (Table A1).

EC-7--Pheochromocytomas in male and female mice occurred with significant positive trends; the incidences in mid and high dose males and in high dose females were significantly greater than those in controls (Table 30). Again, most of the neoplasms were bilateral (Table C1). No increase in the incidence of malignant pheochromocytomas was observed.

Proliferative lesions of the adrenal medulla diagnosed as medullary hyperplasia and pheochromocytoma were part of a morphologic continuum. Medullary hyperplasia consisted of foci of slightly enlarged cells with basophilic cytoplasm arranged in a normal pattern. Pheochromocytomas were larger and caused some compression of adjacent tissue. There was variable but slight alteration of growth pattern, but the cells were similar to those in foci of hyperplasia. Pheochromocytomas were designated as malignant if they obliterated the cortex or penetrated the capsule of the adrenal gland.

Circulatory System

Technical-Grade Pentachlorophenol--The incidence of hemangiosarcomas (all neoplasms were observed in the spleen and liver) in high dose female mice was significantly greater than that in controls (Table 31). Most of these tumors were observed in the spleen. Only 13 spleens of low dose female mice were examined microscopically because hemangiosarcomas are grossly recognizable lesions.

EC-7--The incidences of hemangiosarcomas (observed in the spleen and liver) in high dose female mice were significantly greater than those in controls (Table 31). Only 26 spleens of low dose and 17 spleens of mid dose female mice were examined microscopically.

The hemangiomas and the hemangiosarcomas were characterized by irregular, branching vascular channels that displaced the hepatocellular cords. The hemangiomas consisted of a single layer of relatively well-differentiated endothelial cells lining the vascular channels, whereas the hemangiosarcomas contained endothelial cells that were more pleomorphic and anaplastic.

Spleen: Increased amounts of diffuse hematopoietic cell proliferation in the red pulp were observed at increased incidences in dosed male and high dose female mice receiving technical-grade pentachlorophenol (male: control, 5/30; low dose, 15/23; high dose, 18/46; female: 2/33; 4/13; 11/47).

Nose: Acute focal inflammation of the mucosal glands and focal metaplasia of the olfactory epithelium were observed at increased incidences in high dose mice receiving EC-7 (inflammation--male: control, 4/35; low dose, 1/13; mid dose, 3/16; high dose, 47/49; female: 0/35; 0/14; 2/5; 46/48; focal metaplasia--male: 2/35; 1/13; 2/16; 46/49; female: 1/35; 0/14; 2/5; 45/48). These lesions were not observed in mice that received technical-grade pentachlorophenol.

Mammary Gland: Cystic hyperplasia was observed at an increased incidence in high dose female mice receiving technical-grade pentachlorophenol (control, 7/30; low dose, 0/3; high dose, 20/34).

TABLE 30. ANALYSIS OF ADRENAL GLAND MEDULLARY LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL

	Control	100 ppm	200 ppm	600 ppm
MALE				
TECHNICAL GRADE				
Hyperplasia				
Overall Rates	1/31 (3%)	10/45 (22%)	10/45 (22%)	
Pheochromocytoma (a)				
Overall Rates	0/31 (0%)	10/45 (22%)	23/45 (51%)	
Adjusted Rates	0.0%	37.9%	84.9%	
Terminal Rates	0/12 (0%)	7/23 (30%)	18/22 (82%)	
Day of First Observation		682	549	
Life Table Tests	P<0.001	P=0.021	P<0.001	
Logistic Regression Tests	P<0.001	P=0.017	P<0.001	
Life Table Tests (b)	P<0.001	P<0.001	P<0.001	
Logistic Regression Tests (b)	P<0.001	P<0.001	P<0.001	
DOWICIDE EC-7				
Hyperplasia				
Overall Rates	1/34 (3%)	19/48 (40%)	13/48 (27%)	1/49 (2%)
Pheochromocytoma				
Overall Rates	0/34 (0%)	4/48 (8%)	21/48 (44%)	44/49 (90%)
Adjusted Rates	0.0%	13.8%	67.5%	97.8%
Terminal Rates	0/25 (0%)	3/28 (11%)	19/29 (66%)	34/35 (97%)
Day of First Observation		723	598	458
Life Table Tests	P<0.001	P=0.081	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	P=0.079	P<0.001	P<0.001
Malignant Pheochromocytoma				
Overall Rates	1/34 (3%)	0/48 (0%)	0/48 (0%)	3/49 (6%)
Pheochromocytoma or Malignant Pheochromocytoma (a)				
Overall Rates	1/34 (3%)	4/48 (8%)	21/48 (44%)	45/49 (92%)
Adjusted Rates	4.0%	13.8%	67.5%	100.0%
Terminal Rates	1/25 (4%)	3/28 (11%)	19/29 (66%)	35/35 (100%)
Day of First Observation	727	723	598	458
Life Table Tests	P<0.001	P=0.218	P<0.001	P<0.001
Logistic Regression Tests	P<0.001	P=0.219	P<0.001	P<0.001
Life Table Tests (b)	P<0.001	P=0.109	P<0.001	P<0.001
Logistic Regression Tests (b)	P<0.001	P=0.134	P<0.001	P<0.001

TABLE 30. ANALYSIS OF ADRENAL GLAND MEDULLARY LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (Continued)

	Control	100 ppm	200 ppm	600 ppm
FEMALE				
TECHNICAL GRADE				
Hyperplasia				
Overall Rates	0/33 (0%)	4/48 (8%)	2/49 (4%)	
Pheochromocytoma or Malignant Pheochromocytoma (c)				
Overall Rates	2/33 (6%)	2/48 (4%)	1/49 (2%)	
DOWICIDE EC-7				
Hyperplasia				
Overall Rates	2/35 (6%)	1/49 (2%)	5/46 (11%)	17/49 (35%)
Pheochromocytoma				
Overall Rates	0/35 (0%)	1/49 (2%)	2/46 (4%)	38/49 (78%)
Adjusted Rates	0.0%	3.6%	5.3%	86.3%
Terminal Rates	0/29 (0%)	1/28 (4%)	2/38 (5%)	33/39 (85%)
Day of First Observation		727	727	555
Life Table Tests	P<0.001	P=0.493	P=0.299	P<0.001
Logistic Regression Tests	P<0.001	P=0.493	P=0.299	P<0.001
Malignant Pheochromocytoma				
Overall Rates	0/35 (0%)	1/49 (2%)	0/46 (0%)	1/49 (2%)
Pheochromocytoma or Malignant Pheochromocytoma (c)				
Overall Rates	0/35 (0%)	2/49 (4%)	2/46 (4%)	38/49 (78%)
Adjusted Rates	0.0%	7.1%	5.3%	86.3%
Terminal Rates	0/29 (0%)	2/28 (7%)	2/38 (5%)	33/39 (85%)
Day of First Observation		727	727	555
Life Table Tests	P<0.001	P=0.230	P=0.299	P<0.001
Logistic Regression Tests	P<0.001	P=0.228	P=0.299	P<0.001
Life Table Tests (b)	P<0.001	P=0.436	P<0.548	P<0.001
Logistic Regression Tests (b)	P<0.001	P=0.558	P<0.534	P<0.001

(a) Historical incidence of pheochromocytomas or malignant pheochromocytomas (combined) at study laboratory (mean ± SD): 2/338 (0.6% ± 1%); historical incidence in NTP studies: 30/1,969 (2% ± 2%)
(b) P values vs. combined control group for technical-grade pentachlorophenol and Dowicide EC-7
(c) Historical incidence at study laboratory (mean ± SD): 3/341 (0.9% ± 2%); historical incidence in NTP studies: 22/1,976 (1% ± 2%)

TABLE 31. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL

	Control	100 ppm	200 ppm	600 ppm
TECHNICAL GRADE				
Hemangiosarcoma (a)				
Overall Rates	0/35 (0%)	(b) 3/50 (6%)	6/50 (12%)	
Adjusted Rates	0.0%	6.8%	17.1%	
Terminal Rates	0/29 (0%)	2/41 (5%)	3/32 (9%)	
Day of First Observation		424	694	
Life Table Tests	P=0.013	P=0.194	P=0.029	
Logistic Regression Test	P=0.024	P=0.152	P=0.036	
Life Table Tests (c)	P=0.001	P=0.070	P=0.002	
Logistic Regression Tests (c)	P=0.004	P=0.059	P=0.003	
DOWICIDE EC-7				
Hemangioma				
Overall Rates	0/35 (0%)	(b) 0/50 (0%)	(b) 0/50 (0%)	1/49 (2%)
Hemangiosarcoma				
Overall Rates	0/35 (0%)	(b) 1/50 (2%)	(b) 3/50 (6%)	8/49 (16%)
Adjusted Rates	0.0%	3.6%	7.3%	18.9%
Terminal Rates	0/29 (0%)	1/28 (4%)	1/38 (3%)	5/39 (13%)
Day of First Observation		727	699	611
Life Table Tests	P=0.002	P=0.493	P=0.173	P=0.016
Logistic Regression Tests	P<0.001	P=0.493	P=0.190	P=0.016
Hemangioma or Hemangiosarcoma (a)				
Overall Rates	0/35 (0%)	(b) 1/50 (2%)	(b) 3/50 (6%)	9/49 (18%)
Adjusted Rates	0.0%	3.6%	7.3%	21.3%
Terminal Rates	0/29 (0%)	1/28 (4%)	1/38 (3%)	6/39 (15%)
Day of First Observation		727	699	611
Life Table Tests	P<0.001	P=0.493	P=0.173	P=0.010
Logistic Regression Tests	P<0.001	P=0.493	P=0.190	P=0.010
Life Table Tests (c)	P<0.001	P=0.355	P=0.063	P<0.001
Logistic Regression Tests (c)	P<0.001	P=0.355	P=0.070	P<0.001

(a) Historical incidence of hemangiomas, angiosarcomas, or hemangiosarcomas (combined) at study laboratory (mean ± SD): 7/349 (2% ± 2%); historical incidence in NTP studies: 66/2,040 (3% ± 3%)
(b) Gross lesions and target organs were examined according to protocol (see Table 11).
(c) P values vs. combined control group for technical-grade pentachlorophenol and Dowicide EC-7

Pentachlorophenol (technical grade, 91.6% pure) was tested in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 at doses up to 30 µg/plate with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; no significant increase in the number of revertant colonies was observed in any of the four strains (Table 32). When tested for cytogenetic effects in CHO cells, pentachlorophenol was weakly positive for induction of SCEs (Table 33) and chromosomal aberrations (Table 34). In the SCE test, a weakly positive response was observed within a dose range of 3-30 µg/ml in the absence of S9; in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9, no induction of SCEs by pentachlorophenol was noted. In the test for chromosomal aberration induction, pentachlorophenol gave a negative response without S9 but produced a weakly positive response in the presence of S9, with significant increases in abnormal metaphases at doses of 80 and 100 µg/ml.

TABLE 32. MUTAGENICITY OF PENTACHLOROPHENOL IN *SALMONELLA TYPHIMURIUM* (a)

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

(a) Study performed at EG&G Mason Research Institute. Data presented by Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE 33. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY PENTACHLOROPHENOL (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-Some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c) Summary: Weakly positive								
Dimethyl sulfoxide		50	1,050	413	0.39	8.3	26.0	--
Pentachlorophenol	1	50	1,048	410	0.39	8.2	26.0	98.8
	3	50	1,047	498	0.48	10.0	26.0	120.5
	10	50	1,041	449	0.43	9.0	26.0	108.4
	30	45	939	425	0.45	9.4	28.0	113.3
Triethylenemelamine	0.015	50	1,051	1,506	1.43	30.1	26.0	362.7
+S9 (d) Summary: Negative								
Dimethyl sulfoxide		50	1,049	474	0.45	9.5	26.0	--
Pentachlorophenol	3	50	1,047	555	0.53	11.1	26.0	116.8
	10	50	1,050	523	0.50	10.5	26.0	110.5
	30	50	1,050	529	0.50	10.6	26.0	111.6
	100	50	1,050	548	0.52	11.0	28.0	115.8
Cyclophosphamide	1	50	1,049	1,114	1.06	22.3	26.0	234.7

(a) Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. Data presented in Galloway et al. (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE 34. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY PENTACHLOROPHENOL (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)									
Dimethyl sulfoxide									
	100	2	0.02	2.0					
Pentachlorophenol									
10	100	3	0.03	3.0					
30	100	5	0.05	4.0					
100	100	5	0.05	5.0					
Summary: Negative									
Triethylenemelamine									
0.015	100	25	0.25	22.0					
+S9 (c)									
Dimethyl sulfoxide					*Dimethyl sulfoxide*				
	100	3	0.03	3.0		100	4	0.04	3.0
Pentachlorophenol					Pentachlorophenol				
3	100	5	0.05	5.0	10	100	9	0.09	9.0
10	100	9	0.09	7.0	60	100	14	0.14	10.0
30	100	5	0.05	5.0	70	100	10	0.10	10.0
100	100	65	0.65	33.0	80	100	15	0.15	12.0
Summary: Weakly positive					Summary: Equivocal				
Cyclophosphamide					Cyclophosphamide				
15	100	33	0.33	26.0	15	100	33	0.33	27.0

(a) Study performed at Columbia University. Abs = aberrations. Harvest time--14.0 hours. Data presented in Galloway et al. (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.

(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

IV. DISCUSSION AND CONCLUSIONS

Thirty-Day Studies
Six-Month Studies
Two-Year Studies
Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

These studies were conducted to study the short-term and long-term effects of pentachlorophenol in mice. In addition, the influence of the impurities in pentachlorophenol on toxicity was an important question, since many of these are well-known environmental toxicants (Kimbrough, 1980). Important among these impurities are chlorinated phenols, hexachlorobenzene, and various polychlorinated dibenzodioxins (CDDs) and polychlorinated dibenzofurans (CDFs) (Schwetz et al., 1974). These impurities are formed during the synthesis of pentachlorophenol, vary with the date and source of manufacture (Crosby et al., 1981), and must be removed to produce a "pure" product.

Four grades of pentachlorophenol (technical grade, DP-2, Dowicide EC-7, and pure) were chosen for study; technical-grade pentachlorophenol is representative of the major type used commercially and found in the environment; DP-2 is a more purified grade of pentachlorophenol; EC-7 is a relatively "clean" commercial grade of pentachlorophenol; and pure pentachlorophenol, which is as free of impurities as is practically possible, was used for comparison with the other grades. The technical grade was a composite of three lots from three manufacturers and is representative of what was commercially available at the time that the studies were initiated.

Pentachlorophenol, like chlorinated phenols in general, lacks structurally alerting features (Ashby, 1985; Ashby and Tennant, 1988) which might identify it as a potential electrophilic carcinogen (Miller and Miller, 1977). Further, results of tests with bacteria and with Drosophila indicate that pentachlorophenol, as well as its tetrachlorophenol and hexachlorobenzene impurities, are not gene mutagens. There are indications, however, that both pentachlorophenol and 2,3,5,6-tetrachlorophenol may have some clastogenic potential in mammalian cells. 2,3,4,6-Tetrachlorophenol, hexachlorobenzene, the CDDs, and the CDFs identified as impurities in the technical-grade pentachlorophenol used in the current NTP studies (see Table 3) have been insufficiently tested for determining whether they might have contributed to the weak clastogenicity observed with technical-grade pentachlorophenol.

B6C3F$_1$ mice were chosen for study because the toxicity of the impurities, but not of pentachlorophenol, was well known in this strain (McConnell, 1980) because it is the strain normally used in NTP studies and because the short-term and long-term toxicopathologic effects of various forms of pentachlorophenol were already reported in rats (Schwetz et al., 1978; IPCS, 1987). In addition, it was felt that mice were the best species for use in some of the supplemental studies to be conducted in conjunction with the short-term studies because the methods used were more established for this species. However, the studies in rats may not be adequate for determining the carcinogenic potential of pentachlorophenol because of inadequate numbers of animals per dose group (25) and the lack of a maximum tolerated dose.

The 30-day and 6-month studies were longer than the standard (14-day and 13-week) short-term portions of a National Toxicology Program study. Longer periods were chosen because of the long biologic half-life and the long time necessary to approach a steady-state concentration of several of the impurities (reviewed by Birnbaum, 1985). For example, the biologic half-life of hexachlorodibenzo-*p*-dioxins (HxCDDs) in mice was particularly important in determining doses for the 2-year studies, since maximum tissue levels and attendant toxicity might not be apparent in a 13-week study.

Thirty-Day Studies

Results of the 30-day studies showed that B6C3F$_1$ mice of each sex were fairly resistant to all grades of pentachlorophenol; deaths occurred primarily at 12,500 ppm (1.25%), which corresponds to a daily intake of approximately 1,500 mg/kg. In comparison, the single-administration oral LD_{50} in mice, although variable, is 36-177 mg/kg (IPCS, 1987). Most deaths appeared to be clustered early in the studies (2-4 days) with a second group dying after day 24. According to published reports, the biologic half-life of pentachlorophenol in female mice is approximately 24 hours (Jakobson and Yllner, 1971), with peak concentrations occurring at 4 days. This would correspond to the time of most of the early deaths. A few deaths were also observed at 2,500 ppm (approximately 300 mg/kg per day) in

the EC-7 and pure pentachlorophenol groups. Final mean body weights of mice exposed to either pure pentachlorophenol or EC-7 were decreased (about 10%) in each sex at 2,500 ppm but not at 500 ppm. Again, technical-grade pentachlorophenol was not as potent in this regard, although there was a suggestion of a marginal weight effect (5% decrease) in male mice exposed at 2,500 ppm.

The reason that technical-grade pentachlorophenol was apparently less toxic (based on lethality and weight gain) than EC-7 or pure pentachlorophenol is not known. However, some of the impurities (CDDs and CDFs) are powerful inducers of mixed-function oxidase activity (Goldstein, 1980) and may have stimulated a more rapid metabolism and elimination of pentachlorophenol (Ahlborg and Thunberg, 1978). In summary, the early occurrence of deaths (at 2-4 days) suggests that the toxicity in the 30-day studies was due to pentachlorophenol itself rather than to the impurities. According to Kozak et al. (1979), the mechanism of acute toxicity of all chlorophenols is related to their potential to uncouple oxidative phosphorylation. Pentachlorophenol also binds to mitochondrial proteins and inhibits mitochondrial ATPase activity (Stockdale and Selwyn, 1971a,b). Therefore, the acute toxicity may be related to both activities.

In addition to a decrease in body weight gain, clinical signs of toxicity included weakness, decrease in body temperature, lethargy, and convulsions. However, the latter two effects were observed only in animals that died during the studies. At acutely toxic levels, pentachlorophenol produces neurologic signs in most species in which it has been tested (Renner et al., 1986). Hyperthermia is characteristic of acute toxicity (Borzelleca et al., 1985). The apparent discrepancy between the observed hypothermia in the NTP 30-day studies and previous reports of hyperthermia may lie in the fact that body temperatures were recorded once per week in the NTP studies; the first measurements were not made until after the deaths of numerous animals on days 2 and 4.

In the 30-day studies, the only organ that showed compound-related lesions was the liver. The lesions were characterized by hepatocellular cytomegaly, karyomegaly, nuclear atypia, degeneration, and necrosis. The incidences of the lesions were dose related with all three grades of pentachlorophenol but were more prominent with technical-grade pentachlorophenol. These lesions were less apparent at the highest dose (12,500 ppm), probably because the mice died before the lesions had time to develop fully. At the lowest dose at which lesions were observed (500 ppm), necrosis was not apparent. Overall, the liver lesions were comparable to those that were reported previously in rodents exposed to pentachlorophenol (IPCS, 1987) but also were comparable to those caused by CDDs (McConnell et al., 1978) or CDFs (Moore et al., 1979).

Results of serum biochemical analyses, changes in organ weights and organ to body weight ratios, and results of supplemental liver biochemistry studies correlated well with the histologic observations. Similar chemical-induced hepatic lesions occurred in animals dosed with all three grades of pentachlorophenol. Compared with the centrilobular distribution of these lesions in pure and Dowicide EC-7 pentachlorophenol groups, the liver lesions observed in the animals given technical-grade pentachlorophenol were more diffuse. Liver lesions in animals given Dowicide EC-7 were generally less severe than those in mice given the other two pentachlorophenol preparations.

A top dose of 1,800 ppm was chosen for the 6-month studies of technical-grade pentachlorophenol because of liver lesions and decreased body weight gain in the 2,500-ppm groups with all three grades of pentachlorophenol. The liver lesions at 500 ppm were not life threatening in the 30-day studies and were not expected to be so for a 6-month exposure. Lower top doses were chosen for pure pentachlorophenol (1,500 ppm) and EC-7 (1,200 ppm) because both compounds appeared slightly more toxic than technical-grade pentachlorophenol in the 30-day studies. In addition to pure, EC-7, and technical-grade pentachlorophenol, another grade of pentachlorophenol (DP-2) was used in the 6-month studies. DP-2 represents a grade of pentachlorophenol which has a lower level of impurities (CDDs and CDFs) than technical-grade pentachlorophenol but more than EC-7.

Six-Month Studies

All mice that received 1,800 ppm technical-grade pentachlorophenol died before the end of the studies, but none died at lower doses (600 and 200 ppm). The exact cause of death is not known, but the marked severity of the liver lesions suggests that effects in this organ were at least contributory. Two of 10 male mice exposed to DP-2 at 1,200 ppm died near the end of the studies. None of the other grades of pentachlorophenol caused deaths at the top doses (1,200 or 1,500 ppm).

There was a slight decrease in body weight gain at the top dose of all grades of pentachlorophenol but not at the next lowest dose. Most interesting was the observation that all grades of pentachlorophenol at the lowest dose (200 ppm) (except pure for male mice) actually caused a slight increase in body weight compared with the weights of controls. The cause of this increase is not known, but it appears to be independent of feed consumption.

Compound-related clinical signs were observed only in animals that died. They were comparable to those observed in the 30-day studies, except that convulsions were not observed in the 6-month studies. This would suggest that this abnormality is attributable to pentachlorophenol itself rather than to the impurities. The relatively short biologic half-life of pentachlorophenol (Jakobson and Yllner, 1971) and long latent period (more than 4 months) before death would suggest that the impurities in pentachlorophenol may have contributed to the cause of deaths in the 6-month studies. Further support for this argument was that no signs of toxicity were observed with EC-7 at 1,200 ppm or with pure pentachlorophenol at 1,500 ppm, whereas compound-related deaths were observed in all mice exposed to technical-grade pentachlorophenol at 1,800 ppm and in 2/10 male mice at 1,200 ppm DP-2. The total amount of exposure to all dioxin isomers was 0.4-0.6 mg/kg per day for mice exposed at 1,800 ppm technical-grade pentachlorophenol. Although not directly linear, it is apparent that the level of impurities had a direct impact on the overall toxicity. However, it is also apparent that the presence of the impurities cannot explain all of the toxicity. If so, mice exposed at 600 ppm technical-grade pentachlorophenol should have also died because they consumed more of the toxic impurities than did the mice exposed at 1,200 ppm DP-2.

If HxCDD is used as a measure of concentration of the more toxic impurities, then the total potential exposure of HxCDD at an equivalent dose in male mice exposed at 200 ppm for 6 months was 1.5 µg for technical-grade pentachlorophenol, 0.09 µg for DP-2, and 0.03 µg for EC-7; none was detected in pure pentaclorophenol. The highest total dose of HxCDD (14.3 µg) was in female mice exposed to technical-grade pentachlorophenol at 1,800 ppm. A total dose of 14.3 µg is equivalent to approximately 990 µg/kg, assuming that the average female mouse weighed 23 g during the study and consumed 4.2 g of feed per day. In comparison, the single-administration oral LD_{50} value for male mice is 1,250 µg/kg (probably less for female mice) for the most toxic HxCDD isomer, 1,2,3,6,7,8-HxCDD (McConnell et al., 1978). However, not all the HxCDD in technical-grade pentachlorophenol is composed of the highly toxic isomer. Therefore, it does not seem reasonable that this amount of HxCDD could be the sole cause of the deaths observed in this phase of the studies.

To add to the complexity of the discussion, it is well established that a given amount of CDDs is more toxic if the exposure is spread over a prolonged period than if given in a single dose (McConnell, 1984). The same is probably true for some of the other impurities, such as the CDFs (Moore et al., 1979). The most common explanation for this phenomenon is the relatively poor absorption from the gastrointestinal tract and long biologic half-life of these chlorinated polycyclic compounds (Safe, 1980). Additionally, these same impurities are known to be potent inducers of mixed-function oxidase activity (Goldstein, 1980) and may affect the rates of metabolism and excretion of the impurities and possibly pentachlorophenol itself.

In summary, the most logical explanation for the lethality in mice in the 6-month studies is a result of the toxicity induced by both the impurities and pentachlorophenol. Previous studies (with cattle) designed specifically to evaluate

the impact of the impurities in pentachlorophenol clearly support this view (McConnell et al., 1980). In those studies, technical-grade pentachlorophenol and pure pentachlorophenol were mixed at different ratios so that the cattle all received the same amount of pentachlorophenol (milligram per kilogram), the only difference being the amount of impurities received. Pure pentachlorophenol was minimally toxic after 160 days' exposure, whereas the same amount of technical-grade pentachlorophenol was severely toxic: the animals had severe depression of body weight gain and feed conversion and had marked lesions, particularly in the urinary tract and biliary system. The authors of this study concluded "that the toxicity of pentachlorophenol in cattle is primarily attributable to its contamination with toxic impurities."

Results of various hematologic analyses in the 6-month NTP studies in mice showed biologically significant effects on erythrocytes, as evidenced by a marginal decrease in hematocrit and erythrocyte counts and an increase in erythrocyte volume. These effects were seen only in mice exposed to DP-2 or technical-grade pentachlorophenol and in total were evaluated as a mild macrocytic anemia. The increase in circulating reticulocytes was interpreted as a response to the anemia. Anemia has not been reported in mice exposed to pentachlorophenol but has been observed after exposure to CDDs (McConnell et al., 1978). Since it was found only in animals exposed at the higher levels of these impurities, it seems reasonable to ascribe the anemia to them rather than to pentachlorophenol itself.

Prominent increases in both the absolute liver weight and the liver weight to body weight ratio were dose related in male and female mice exposed to all types of pentachlorophenol. This effect was more prominent in animals that received greater amounts of impurities, even at the same dose of pentachlorophenol. However, it was also clearly present in mice that were exposed to pure pentachlorophenol. In previous studies using other mammalian species, a similar effect on the liver was often found (McConnell, 1980). The cause of the enlargement is probably related to hepatocellular hypertrophy (cytomegaly). The basis of the hepatocellular enlargement has been reported to be due primarily to marked proliferation of endoplasmic reticulum, especially of the smooth type (McConnell, 1980), as would be expected in light of the marked effects on mixed-function oxidase activity (see below).

The spleen weight (actual and relative to body weight) was increased in a dose-related fashion in male mice with all types of pentachlorophenol. In contrast, the spleen was smaller in female mice in the high dose groups of technical-grade pentachlorophenol, DP-2, and EC-7. Decreases in spleen weight were reported in short-term studies of CDDs (McConnell et al., 1978). Thymus weights were not affected by exposure to any of the types of pentachlorophenol used in the 6-month studies. This observation was surprising in light of the fact that reduced thymus weight appears to be one of the most sensitive indicators of dioxin or dibenzofuran exposure in all species of animals, including mice (McConnell, 1984). One possible explanation is that the thymus has already undergone a significant amount of normal involution in an 8-month-old mouse.

The only serum chemistry values that were abnormal in male and female mice were alanine aminotransferase (glutamic-pyruvic transaminase) and aspartate aminotransferase (glutamic-oxaloacetic transaminase). Alanine aminotransferase was increased at the highest doses of all grades of pentachlorophenol, and aspartate aminotransferase was increased at the highest doses of DP-2 and technical-grade pentachlorophenol. Increases in the activity of these enzymes are thought to be related to hepatocellular damage and necrosis with subsequent release of the enzymes into the general circulation. A similar explanation is probably relevant for the increased levels of γ-glutamyl transpeptidase in male mice, but isozyme separation would be required to confirm this.

Histopathologically, the organ that showed the most severe lesions in the 6-month studies was the liver. Qualitatively, the lesions were comparable to those observed in the 30-day studies, with cytomegaly and karyomegaly being most prominent at lower doses and inflammation and necrosis superimposed at higher doses. Necrosis was more severe in the mice that died and may

have contributed to their death. One lesion that was directly related to the level of impurities (in the sense that it was more apparent in mice exposed to technical-grade pentachlorophenol) and that was not present in the 30-day studies was intrahepatic bile duct hyperplasia. Pigmentation was observed in mice exposed to all grades of pentachlorophenol. The influence of the halogenated polycyclic impurities (CDDs and CDFs) on pathologic effects on the liver would be predicted to be more prominent in the 6-month studies than in the 30-day studies because of the relatively long biologic half-life of the impurities compared with that of pentachlorophenol itself (Birnbaum, 1985).

Subtle pigmentation similar in staining characteristics to that observed in the liver was observed in the epithelium lining the urinary bladder. The pigment did not appear to cause any concomitant lesion in the urinary bladder.

An unusual (and unexpected) metaplastic lesion was observed in the epithelial lining of the nasal cavity of male and female mice exposed to pure pentachlorophenol or EC-7 and, to a lesser extent, of females exposed to DP-2. The lesion was characterized as an increase in the number of goblet cells and flattening of the epithelium and, although not of marked severity, was qualitatively similar to what is seen after prolonged exposure to irritating chemicals such as formaldehyde (Swenberg et al., 1983). A small amount of pentachlorophenol will vaporize at ambient temperatures (KP_a at 20° C is 2×10^{-6} mm mercury; Zimmerli, 1982), and it is possible that it could have been present at irritating levels in the semi-enclosed environment of the cages (polycarbonate shoe-box type). However, this lesion was not observed in mice exposed to technical-grade pentachlorophenol or DP-2, for which all other experimental conditions were the same, or in other studies of pentachlorophenol (IPCS, 1987).

There did not appear to be a consistent sex specificity for any of the above-mentioned lesions in the 6-month studies. This is consistent with previous reports (IPCS, 1987). However, most of the toxic impurities (CDDs and CDFs) have been found to be more toxic in females than in males in most species, both in experimental studies and and in incidents of accidental exposure (McConnell, 1984). Several studies (Poland and Kimbrough, 1984) have shown a complex interaction of dioxins and endocrine pathways, which may explain this preferential toxicity.

The induction of hepatic AHH activity in the 6-month studies indicates that the contribution of CDDs to the hepatic effects of EC-7 is similar to that of the "pure" grade of pentachlorophenol. Even more important, there is a greater than tenfold difference in the dose-response curves for EC-7 and technical-grade pentachlorophenol on AHH activity.

A previous study demonstrated that feeding technical-grade pentachlorophenol (500 ppm for 8 months) to female Sprague Dawley rats produced porphyria after 8 months' exposure, whereas pure pentachlorophenol had no effect (Goldstein et al., 1977), suggesting that the porphyria was due to the presence of CDDs and CDFs. This was consistent with the known porphyrogenic effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Goldstein et al., 1973, 1982). Somewhat surprisingly, technical-grade pentachlorophenol did not cause symptoms of overt porphyria in the present studies, although very minimal increases in hepatic porphyrins were observed with several grades of pentachlorophenol. These results may simply indicate that this strain of mice is less sensitive to the porphyrogenic effects of halogenated dibenzodioxins than are female Sprague Dawley rats. This possibility is also suggested by the fact that a threefold to tenfold higher dose of polybrominated biphenyls was required to produce porphyria in $B6C3F_1$ mice than in F344 female rats (Gupta et al., 1983).

The immunologic effects associated with exposure to pentachlorophenol, particularly technical grade, were characterized by suppression of humoral-mediated (i.e., antibody) responses. These observations are consistent with those from other studies in mice, demonstrating that technical-grade pentachlorophenol causes a marked effect on humoral-mediated immunity without suppressing cell-mediated immunity (Kerkvliet et al., 1982a,b; Holsapple et al., 1984). A similar effect also occurs in adult mice

following acute TCDD exposure (Luster et al., 1987). These studies also showed that exposure to a more pure grade of pentachlorophenol (e.g., EC-7) was not immunosuppressive, suggesting that the impurities in technical-grade pentachlorophenol mediate the immunosuppression. This was confirmed in subsequent studies with impurity fractions extracted from technical-grade pentachlorophenol (Kerkvliet et al., 1985). These data demonstrated that the chlorinated dioxin/furan fraction, and not the chlorinated phenoxyphenol or diphenyl ether fraction, expressed the immunosuppressive activity. Within the immunotoxic fraction, 1,2,3,6,7,8-hexachlorodibenzodioxin, 1,2,3,4,6,7,8-heptachlorodibenzodioxin, and 1,2,3,4,6,7,8-heptachlorodibenzofuran all demonstrated immunosuppressive activity. Coadministration of these three compounds at dose levels found in technical-grade pentachlorophenol produced the same degree of suppression that occurred following administration of technical-grade pentachlorophenol, further supporting the concept that the impurities were responsible for the toxicity. As with TCDD (Luster et al., 1987), immunosuppression by technical-grade pentachlorophenol is also mediated through the *Ah* receptor (Kerkvliet et al., 1985). In the present studies, suppression of humoral immunity also occurred after exposure to several grades of pentachlorophenol and was consistent with the presence of impurities in these preparations.

Based on the observations mentioned above, economic considerations (cost of conducting the 2-year studies), and the results of previous studies of various grades of pentachlorophenol (IPCS, 1987), technical-grade pentachlorophenol and EC-7 were selected for the 2-year carcinogenesis studies. Technical-grade pentachlorophenol was chosen because it represents the material generally used commercially and is the substance to which most people are exposed. EC-7 was chosen because it contains the lowest level of toxic impurities (next to pure pentachlorophenol) and yet represents a practical alternative to technical-grade pentachlorophenol. In addition, the results of the 6-month studies suggested that EC-7 would behave similarly (toxicologically) to pure pentachlorophenol in a 2-year study. Subsequent to the selection of these two grades of pentachlorophenol and the start of the studies, EC-7 was taken out of production, and today it is no longer used commercially. The doses selected for the 2-year studies were based on the hypothesis that the highest dose should cause chemical-related lesions but not death, except from neoplastic lesions (NTP, 1984). In addition, the doses were selected in an effort to evaluate the influence of the impurities on the long-term toxicity of pentachlorophenol, especially carcinogenic activity.

Two-Year Studies

In the 2-year studies, fewer mice were used in the control groups (35) than in the dosed groups (50); it was felt that the control groups could be combined for statistical purposes, even though the studies were started 1 month apart.

Body weight gain in male mice did not appear to be affected for most of the study by exposure to either technical-grade pentachlorophenol (100 or 200 ppm) or EC-7 (100, 200, or 600 ppm). At most time points, the male mice exposed to technical-grade pentachlorophenol actually weighed slightly more than the controls, but they also weighed slightly more at the start of the study. However, at the highest dose of both compounds, female mice did not gain weight as rapidly as did controls after week 45, although in neither case was the body weight gain reduced to the extent that it would be life threatening. The cause of the decreased weight gain was not determined but was not attributed to decreased feed intake.

An important observation was the marked difference in survival between the two male control groups: 12/35 for the technical-grade pentachlorophenol study vs. 25/35 for EC-7. The survival of the latter group (71%) is similar to that in other NTP studies of $B6C3F_1$ mice (Haseman et al., 1985). Survival of the two male control groups was similar for about 1 year, after which a gradual and increasing divergence was observed. Thus, the two control groups are also combined for evaluation of the carcinogenic activity of both compounds. Survival of the female control groups (29/35 and 29/35) was similar to that of historical controls.

Although the survival of male mice exposed to technical-grade pentachlorophenol (100 ppm,

48%; 200 ppm, 44%) was greater than that of controls (34%), both were somewhat lower than that of historical controls (Haseman et al., 1985). Some of the deaths in the dosed groups may have been related to neoplastic effects or general toxicity in the liver. In contrast, survival of female mice exposed to technical-grade pentachlorophenol was not affected except minimally at the highest dose late in the study (after week 96), and yet they showed similar lesions.

Survival of the mice exposed at the high dose of EC-7 was actually greater than that of the low dose groups (male: control, 71%; 100 ppm, 56%; 200 ppm, 58%; 600 ppm, 70%; female: 83%; 56%; 76%; 78%). In all cases survival was adequate to evaluate the carcinogenic activity.

The nonneoplastic effects described in the 6-month studies were duplicated in the 2-year studies of both compounds. These effects included inflammation, necrosis, cytomegaly, pigmentation, and bile duct proliferation in the liver. In addition, clear cell foci and an increased amount of extramedullary hematopoiesis were observed in the liver of exposed mice. The only nonneoplastic liver lesion that was clearly related to the level of impurities was bile duct hyperplasia. The incidence of this lesion in the technical-grade pentachlorophenol male (but not female) mice was markedly greater than the incidences in the EC-7 groups at the same dose. It should be noted that the liver lesions occurred even at the lowest doses used in the 2-year studies.

A comparison of effects at equal doses suggests that bile duct hyperplasia (as noted in the 6-month studies) in males and females and possibly some of the other hepatic lesions in females (see Table 28) may be related to exposure to the impurities at a higher level rather than to pentachlorophenol itself. This observation is supported by numerous other studies that have reported these same lesions after mice were exposed to CDDs and CDFs (McConnell, 1984).

Another noteworthy compound-related lesion was brownish pigmentation in several organs in addition to the liver. This lesion was dose related and was more apparent in males than in females and in mice exposed at a higher level of impurities. It is suggested that the pigment is related to an excess of porphyrin pigments, although porphyrins were either not, or only slightly, elevated in the liver in the 6-month studies. Special histochemical staining procedures would be required to definitely resolve this point.

Hyperplasia and metaplasia of the nasal mucosa were observed in the 2-year studies (as in the 6-month studies) only in mice exposed to EC-7 and were clearly dose related, being found at high incidences only at 600 ppm. As mentioned previously, the etiology of this lesion is not known.

Compound-related neoplastic effects were observed in three organs: liver, adrenal medulla, and spleen. The incidences of hepatocellular neoplasms were increased in male mice exposed to either technical-grade pentachlorophenol or EC-7 at all doses, although at a given dose of pentachlorophenol, the incidences were lower in the mice exposed to EC-7 than to technical-grade pentachlorophenol. In contrast, the incidences of liver neoplasms in female mice exposed to technical-grade pentachlorophenol, although increased, were not as dramatic as in male mice. This is another indication that male mice were possibly more susceptible than females to the toxicity of pentachlorophenol in these studies. Significantly increased incidences ($P<0.001$) of liver neoplasms in female mice occurred only at the highest dose (600 ppm) of EC-7, whereas the incidence in the 200-ppm group of female mice (12%) was not much greater than the historical control incidence (8%) for this laboratory. Importantly, although increased incidences of liver neoplasms were observed in dose groups showing nonneoplastic "toxic" lesions, no increase was found in the next lowest dose group (200 ppm), although hepatocellular toxicity of identical morphology and approximately equal severity was observed.

Benign neoplasms of the adrenal medulla (pheochromocytomas) were observed at increased incidences in male mice exposed to either technical-grade pentachlorophenol (both doses) or EC-7 (highest two doses). Most of these neoplasms were small (less than 5 mm in diameter), and several were observed only microscopically. A majority of mice showing this lesion had

bilateral involvement. Focal hyperplasia, which is considered part of the neoplastic continuum for adrenal medullary neoplasms, was also increased. At comparable pentachlorophenol exposure concentrations in male mice, the incidences of pheochromocytomas were approximately equal at 200 ppm (technical-grade pentachlorophenol, 51% vs. EC-7, 44%) but at 100 ppm, the incidence was somewhat lower in mice exposed to EC-7 (8% vs. 22%). In females, a significant increase in the incidence of pheochromocytomas was observed only in the highest dose group (600 ppm) exposed to EC-7 and not in either dose group (100 or 200 ppm) exposed to technical-grade pentachlorophenol. Pheochromocytomas have not been reported as a result of exposure to pentachlorophenol in other long-term studies (IPCS, 1987). However, in a study reported by Schwetz et al. (1978), an increased incidence of these neoplasms was observed in male Sprague Dawley rats fed EC-7 at 1, 3, 10, or 30 mg/kg per day for 22-24 months; the incidences were 3/37 (control), 6/26, 7/27, 5/27, and 5/27, respectively. No increase was observed in female rats exposed at the same doses in that study (1/26; 0/24; 0/25; 2/24; 0/24) (R.J. Kociba, Dow Chemical Co., personal communication, 1988).

Hemangiosarcomas involving the spleen and liver were observed at increased incidences in female mice exposed at the highest dose of both technical-grade pentachlorophenol (200 ppm, 12%) and EC-7 (600 ppm, 16%). These neoplasms were primarily recognized at necropsy, especially in the spleen. Therefore, the spleen at lower doses was not examined histopathologically unless a visible lesion was noted at necropsy (McConnell, 1983b). Endothelial tumors were not observed at an increased incidence in male mice exposed to either technical-grade pentachlorophenol or EC-7. Hemangiosarcomas have not been reported to be a result of pentachlorophenol exposure or exposure to pentachlorophenol impurities in previous carcinogenesis studies (NCI, 1980; IPCS, 1987).

As noted in the Introduction, these studies were designed to evaluate the toxicity of pentachlorophenol in B6C3F$_1$ mice and to determine the role of the impurities in the toxic syndrome. The first question was adequately addressed in the 30-day, 6-month, and 2-year studies. Major compound-related effects were observed in the liver, spleen, adrenal glands, nasal cavity, and immune system.

The second question is more complex. In the 30-day studies, deaths that occurred 2-4 days after exposure were ascribed to the direct action of pentachlorophenol, probably related to its potential to uncouple oxidative phosphorylation, with attendant characteristic clinical signs. The 6-month studies of four grades of pentachlorophenol showed the clinicopathologic syndrome to be more pronounced with increasing levels of the impurities. The lesions in the liver were comparable to those reported for pentachlorophenol (IPCS, 1987) but also for the impurities (McConnell, 1984).

In the 2-year studies, the neoplastic effects of pentachlorophenol can be distinguished from those of its impurities as follows. Clearly, both grades of pentachlorophenol (technical grade and EC-7) used in these studies were carcinogenic in B6C3F$_1$ mice. Although the liver neoplasms and other morphologic changes in the liver are comparable to those observed in this strain of mouse in carcinogenesis studies of two dibenzo-*p*-dioxins (TCDD and HxCDD), the dose response suggests that pentachlorophenol itself was involved in their causation. An additional attempt to sort out the influence of pentachlorophenol vs. its contaminants, specifically HxCDD, in the induction of liver neoplasms in male mice is presented in Figure 13 and Table 35. The approximate amount of HxCDD consumed per week in the pentachlorophenol study was compared with that in the HxCDD study (NCI, 1980). For this exercise, two assumptions were made, both of which are imperfect (but hopefully, minimally). First, exposure to HxCDD in the pentachlorophenol feed study was assumed to be comparable to that in the NCI corn oil gavage HxCDD study. Second, the HxCDD isomers in the pentachlorophenol study were assumed to be equitoxic to the HxCDD in the NCI study.

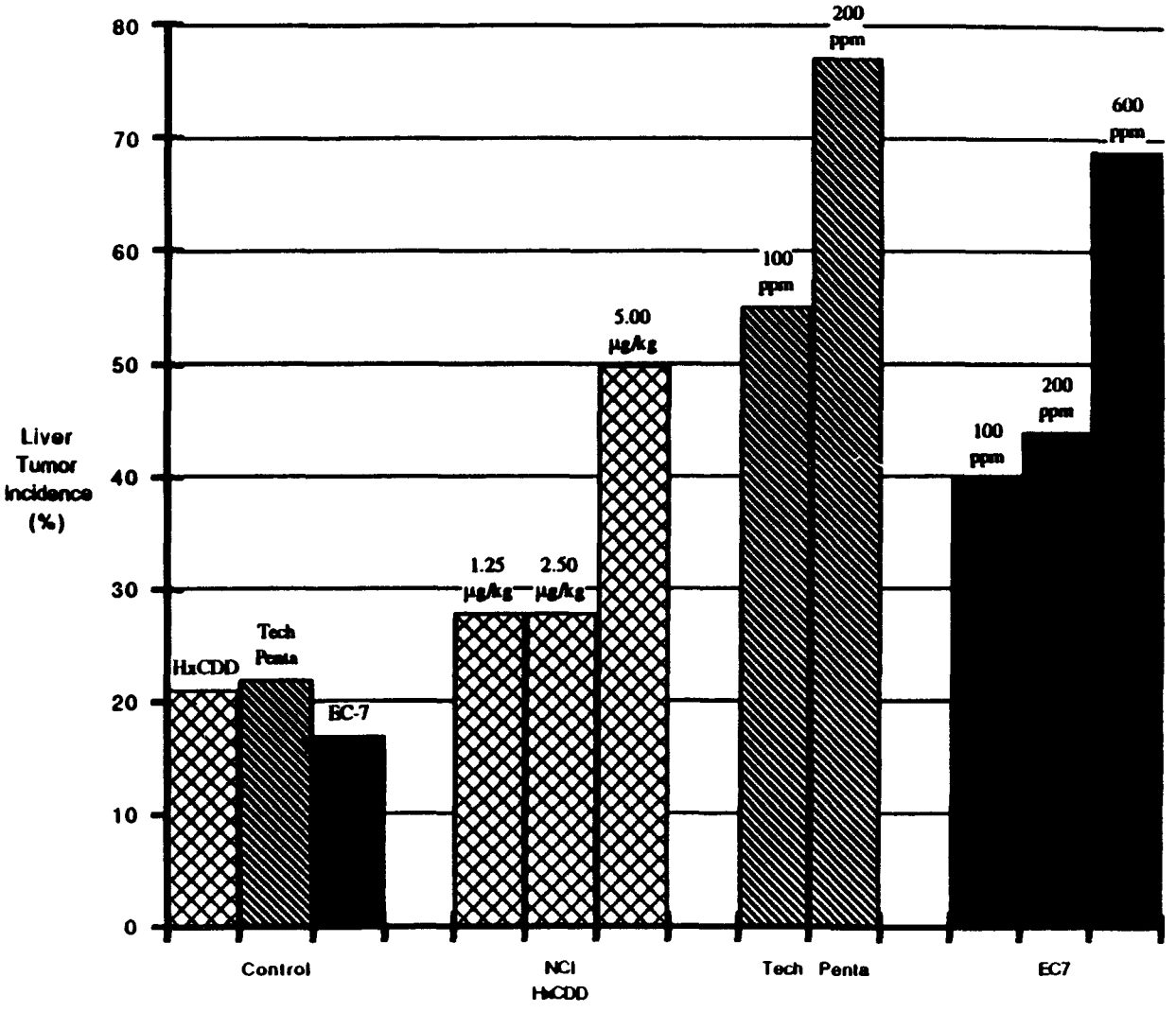


FIGURE 13. COMPARISON OF LIVER NEOPLASM INCIDENCES IN MALE B6C3F$_1$ MICE IN THE HEXACHLORODIBENZO-*p*-DIOXIN STUDIES AND IN THE PENTACHLOROPHENOL STUDIES

TABLE 35. COMPARISON OF LIVER NEOPLASM INCIDENCES IN MALE B6C3F$_1$ MICE IN THE HEXACHLORODIBENZO-*p*-DIOXIN STUDIES AND IN THE PENTACHLOROPHENOL STUDIES (a)

HxCDD		Technical-Grade Pentachlorophenol			EC-7		
Dose of HxCDD (µg/kg per week)	Incidence of Liver Tumors (percent)	Conc. of Technical-Grade Pentachlorophenol in Feed (ppm)	Dose of HxCDD (µg/kg per week)	Incidence of Liver Tumors (percent)	Conc. of EC-7 in Feed (ppm)	Dose of HxCDD (µg/kg per week)	Incidence of Liver Tumors (percent)
0	21	0	0	22	0	0.000	17
1.25	28	100	0.77	55	100	0.014	40
2.5	28	200	1.54	77	200	0.028	44
5	50	--	--	--	600	0.070	69

(a) Hexachlorodibenzo-*p*-dioxin = HxCDD; NCI hexachlorodibenzo-*p*-dioxin studies (NCI, 1980) and current NTP pentachlorophenol studies.

From Table 35, it is clear that exposure to relatively pure pentachlorophenol (EC-7), technical-grade pentachlorophenol, or HxCDD causes liver neoplasms in male mice. The data also show that at equal doses of pentachlorophenol, a higher incidence of liver neoplasms was observed with technical-grade pentachlorophenol than with EC-7. However, it is also clear that the HxCDD alone accounts for only a small part of the liver tumor response. Therefore, in male mice, the data suggest that pentachlorophenol itself is carcinogenic to the liver and that HxCDD probably only accentuates the response. In addition, neoplasms of the adrenal medulla and of the endothelium (hemangiosarcomas) were not observed in earlier studies of the impurities (NCI, 1980; NTP, 1982) and therefore must have been caused by pentachlorophenol itself.

In summary, a reasonable conclusion from the data in these studies is that pentachlorophenol is primarily responsible for the carcinogenic response in mice but that the impurities may possibly play a small part in the neoplastic process, at least in the liver of male mice. Importantly, the grade of pentachlorophenol currently found in commercial use invariably contains impurities at levels similar to those found in these studies.

Audit

The experimental and tabulated data for the NTP Technical Report on pentachlorophenol were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix J, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

IV. DISCUSSION AND CONCLUSIONS

Conclusions

Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity** for male B6C3F$_1$ mice fed diets containing technical-grade pentachlorophenol, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms. There was *some evidence of carcinogenic activity* for female B6C3F$_1$ mice exposed to technical-grade pentachlorophenol, as shown by increased incidences of hemangiosarcomas and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* for male B6C3F$_1$ mice exposed to pentachlorophenol, EC-7, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms. There was *clear evidence of carcinogenic activity* for female B6C3F$_1$ mice exposed to pentachlorophenol, EC-7, as shown by increased incidences of adrenal medullary and hepatocellular neoplasms and hemangiosarcomas.

Chemically related increased incidences of nonneoplastic lesions in mice of each sex included hepatocellular cytomegaly, necrosis, inflammation, pigmentation, and clear cell foci and intrahepatic bile duct hyperplasia.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 9.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 12-13.

V. REFERENCES

V. REFERENCES

1. Abbritti, G.; DeMatteis, F.D. (1971-1972) Decreased levels of cytochrome P-450 and catalase in hepatic porphyria caused by substituted acetamides and barbiturates. Chem. Biol. Interact. 4:281-286.

2. Adema, D.M.M.; Vink, G.J. (1981) A comparative study of 1,1,2-trichloroethane, dieldrin, pentachlorophenol, and 3,4-dichloroaniline for marine and fresh water organisms. Chemosphere 10:533-554.

3. Ahlborg, U.G.; Thunberg, T. (1978) Effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the *in vivo* and *in vitro* dechlorination of pentachlorophenol. Arch. Toxicol. 40:55-61.

4. Ahlborg, U.G.; Thunberg, T.M. (1980) Chlorinated phenols: Occurrence, toxicity, metabolism, and environmental impact. CRC Crit. Rev. Toxicol. 7:1-35.

5. Allain, C.C.; Poon, L.S.; Chan, C.S.G.; Richmond, W.; Fu, P.C. (1974) Enzymatic determination of total serum cholesterol. Clin. Chem. 20:470-475.

6. Amer, S.M.; Ali, E.M. (1968) Cytological effects of pesticides. II. Meiotic effects of some phenols. Cytologia 33:21-33.

7. Amer, S.M.; Ali, E.M. (1969) Cytological effects of pesticides. IV. Mitotic effects of some phenols. Cytologia 34:533-540.

8. American Conference of Governmental Hygienists (ACGIH) (1980)

9. Ames, B.N.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

10. Anderson, K.J.; Leighty, E.G.; Takahashi, M.T. (1972) Evaluation of herbicides for possible mutagenic properties. J. Agric. Food Chem. 20:649-656.

11. Angerer, C. (1984) Production and use of pentachlorophenol in the Federal Republic of Germany. Pentachlorphenol - Specimen Case. Report No. 106 04 007. Berlin: UBA F&E. 76 p.

12. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

13. Arrhenius, E.; Renberg, L.; Johansson, L. (1977a) Subcellular distribution, a factor in risk evaluation of pentachlorophenol. Chem. Biol. Interact. 18:23-34.

14. Arrhenius, E.; Renberg, L.; Johansson, L.; Zetterqvist, M.A. (1977b) Disturbance of microsomal detoxication mechanisms in liver by chlorophenol pesticides. Chem. Biol. Interact. 18:35-46.

15. Ashby, J. (1985) Fundamental structural alerts to potential carcinogenicity and noncarcinogenicity. Environ. Mutagen. 7:919-921.

16. Ashby, J.; Tennant, R.W. (1988) Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat. Res. 204:17-115.

17. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

18. Birnbaum, L.S. (1985) The role of structure in the disposition of halogenated aromatic xenobiotics. Environ. Health Perspect. 61:11-20.

19. Blackman, G.E.; Parke, M.H.; Garton, G. (1955) The physiological activity of substituted phenols. II. Relationships between physical properties and physiological activity. Arch. Biochem. Biophys. 54:55-71.

20. Blevins, D. (1965) Pentachlorophenol poisoning in swine. Vet. Med. 60:455.

21. Boorman, G.A.; Montgomery, C.A., Jr.; Eustis, S.L.; Wolfe, M.J.; McConnell, E.E.; Hardisty, J.F. (1985) Quality assurance in pathology for rodent carcinogenicity studies. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

22. Borzelleca, J.F.; Hayes, J.R.; Condie, L.W.; Egle, J.L., Jr. (1985) Acute toxicity of monochlorophenols, dichlorophenols, and pentachlorophenol in the mouse. Toxicol. Lett. 29:39-42.

23. Boyle, T.P.; Robinson-Wilson, E.F.; Petty, B.D.; Weber, W. (1980) Degradation of pentachlorophenol in simulated lentic environment. Bull. Environ. Contam. Toxicol. 24:177-184.

24. Braun, W.H.; Sauerhoff, M.W. (1976) The pharmacokinetic profile of pentachlorophenol in monkeys. Toxicol. Appl. Pharmacol. 38:525-533.

25. Braun, W.H.; Young, J.D.; Blau, G.E.; Gehring, P.J. (1977) The pharmacokinetics and metabolism of pentachlorophenol in rats. Toxicol. Appl. Pharmacol. 41:395-406.

26. Braun, W.H.; Blau, G.E.; Chenoweth, M.B. (1979) The metabolism/pharmacokinetics of pentachlorophenol in man, and a comparison with the rat and monkey. Deichmann, W.B., Ed.: Toxicology and Occupational Medicine. New York: Elsevier/North-Holland, pp. 289-296.

27. Buikema, A.L.; Ginniss, M.J.; Cairns, J. (1979) Phenolics in aquatic ecosystems: A selected review of recent literature. Mar. Environ. Res. 2:87-181.

28. Buser, H.R. (1982) Report on the Formation of PCDDs During Pyrolysis of PCP and PCP-Na. Unpublished Report. Wadenswil, Switzerland: Eidg. Forschungsanstalt. 2 p.

29. Carlson, G.P.; Smith, E.N.; Johnson, K.M. (1980) Induction of xenobiotic metabolism in rat liver by chlorinated diphenyl ether isomers. Drug Chem. Toxicol. 3:293-303.

30. Casto, B.C. (1981) Effect of chemical carcinogens and mutagens on the transformation of mammalian cells by DNA viruses. Gauri, K.K., Ed.: Antiviral Chemotherapy: Design of Inhibitors of Viral Functions. New York: Academic Press, pp. 261-278.

31. Cirelli, D.P. (1978) Patterns of pentachlorophenol usage in the United States of America: An overview. Rao, K.R., Ed.: Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology. New York: Plenum Press, pp. 13-18.

32. Cleveland, L.; Buckler, D.R.; Mayer, F.L.; Branson, D.R. (1982) Toxicity of three preparations of pentachlorophenol to fathead minnows: A comparative study. Environ. Toxicol. Chem. 1:205-212.

33. Courtney, K.D.; Moore, J.A. (1971) Teratology studies with 2,4,5-trichlorophenoxyacetic acid and 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol. Appl. Pharmacol. 20:396-403.

34. Courtney, K.D.; Copeland, M.F.; Robbins, A. (1976) The effects of pentachloronitrobenzene, hexachlorobenzene, and related compounds on fetal development. Toxicol. Appl. Pharmacol. 35:239-256.

35. Cox, D.R. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

36. Crosby, D.G.; Beynon, K.I.; Greve, P.A.; Korte, F.; Still, G.G.; Vouk, J.W. (1981) Environmental chemistry of pentachlorophenol. Pure Appl. Chem. 53:1051-1080.

37. Cserjesi, A.J. (1972) Detoxification of chlorinated phenols. Int. Biodeterioration Bull. 8:135-138.

38. Curtis, R.F.; Land, D.G.; Griffith, N.M.; Gee, M.; Robinson, D.; Peel, J.L.; Dennis, C.; Gee, J.M. (1972) 2,3,4,6-Tetrachloroanisole association with musty taint in chickens and microbiological formation. Nature 235:223.

39. Demidenko, N.M. (1969) Materials for establishing the maximum permissible concentrations in air. Gig. Tr. Prof. Zabol. 7:58-60.

40. Dijk, J.J.; Van der Meer, C.; Wijnans, M. (1977) The toxicity of sodium pentachlorophenolate for three species of decapod crustaceans and their larvae. Bull. Environ. Contam. Toxicol. 17:622-630.

41. Dinse, G.E.; Haseman, J.K. (1986) Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. Fundam. Appl. Toxicol. 6:44-52.

V. REFERENCES

42. Dinse, G.E.; Lagakos, S.W. (1983) Regression analysis of tumour prevalence data. J. R. Stat. Soc. C32:236-248.

43. Duggan, R.E.; Corneliussen, P.E. (1972) Dietary intake of pesticide chemicals in the United States. III. June 1968 - April 1970. Pestic. Monit. J. 5:331-341.

44. Dunn, O.J. (1964) Multiple comparisons using rank sums. Technometrics 6:241-252.

45. Dunnett, C.W. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50:1096-1122.

46. Edwards, M.J. (1968) Congenital malformations in the rat following induced hyperthermia during gestation. Teratology 1:173-178.

47. Exon, J.H.; Koller, L.D. (1983a) Effects of chlorinated phenols on immunity in rats. Int. J. Immunopharmacol. 5:131-136.

48. Exon, J.H.; Koller, L.D. (1983b) Alternation of transplacental carcinogenesis by chlorinated phenols. Jolley, R.L.; et al., Eds.: Water Chlorination: Environmental Impact and Health Effects, Vol. 2, Book 4. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., pp. 1177-1188.

49. Fahrig, R. (1974) Comparative mutagenicity studies with pesticides. IARC Scientific Publications 10:161-181.

50. Fahrig, R.; Nilsson, C.-A.; Rappe, C. (1978) Genetic activity of chlorophenols and chlorophenol impurities. Rao, K.R., Ed.: Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology. New York: Plenum Press, pp. 325-338.

51. Federal Register (Fed. Regist.) (1977) Gelatin: Affirmation of GRAS status as a direct and indirect human food ingredient. 42:58763-58765.

52. Federal Register (Fed. Regist.) (1984) Environmental Protection Agency: Pentachlorophenol: Preliminary notice of determination concluding the rebuttable presumption against registration of pesticide products containing pentachlorophenol for non-wood preservative uses; proposed notice of intent to cancel such registrations; notice of availability of position document 2/3. 50:1978-2006.

53. Federal Register (Fed. Regist.) (1988) Environmental Protection Agency: Pentachlorophenol products; amendment of notice of intent to cancel registrations of products for non-wood biocide uses. 53:5524-5535.

54. Fischer, M. (1983) Pentachlorophenol as Model Case of a Xenobiotic Compound. Research Report No. 10604007. Berlin: Federal Health Office Institute for Water, Soil and Air Hygiene. 38 p.

55. Friedman, M.A.; Watt, K.M.; Higgins, E.S. (1977) In vitro and in vivo effects of dimethylnitrosamine on mouse liver mitochondrial function. Proc. Soc. Exp. Biol. Med. 154:530-533.

56. Galloway, S.M.; Bloom, A.D.; Resnick, M.; Margolin, B.H.; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

57. Galloway, S.M.; Armstrong, M.J.; Reuben, C.; Colman, S.; Brown, B.; Cannon, C.; Bloom, A.D.; Nakamura, F.; Ahmed, M.; Duk, S.; Rimpo, J.; Margolin, B.H.; Resnick, M.A.; Anderson, B.; Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Molec. Mutagen. 10(Suppl. 10):1-175.

58. Gart, J.J.; Chu, K.C.; Tarone, R.E. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

59. Gebefuegi, I.; Parlar, H.; Korte, F. (1979) Occurrence of pentachlorophenol in closed environments. Ecotoxicol. Environ. Safety 3:269.

60. Gielen, J.E.; Gorifon, F.M.; Nebert, D.W. (1972) J. Biol. Chem. 247: 1125.

61. Goldstein, J.A. (1980) Structure-activity relationships for the biochemical effects and the relationship to toxicity. Kimbrough, R.D., Ed.: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 151-190.

62. Goldstein, J.A.; Hickman, P.; Bergman, H.; Vos, J.G. (1973) Hepatic porphyria induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the mouse. Res. Commun. Chem. Pathol. Pharmacol. 6:919-928.

63. Goldstein, J.A.; Friesen, M.; Linder, R.E.; Hickman, P.; Hass, J.R.; Bergman, H. (1977) Effects of pentachlorophenol on hepatic drug-metabolizing enzymes and porphyria related to contamination with chlorinated dibenzo-*p*-dioxins and dibenzofurans. Biochem. Pharmacol. 26:1549-1557.

64. Goldstein, J.A.; Linko, P.; Bergman, H. (1982) Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Biochem. Pharmacol. 31:1607-1613.

65. Guerzoni, M.E.; Del Cupolo, L.; Ponti, I. (1976) Mutagenic activity of pesticides. Riv. Sci. Tecn. Alimenti Nutri. Um. 6:161-165.

66. Gupta, B.N.; McConnell, E.E.; Goldstein, J.A.; Harris, M.W.; Moore, J.A. (1983) Effects of a polybrominated biphenyl mixture in the rat and mouse. Six-month studies. Toxicol. Appl. Pharmacol. 68:1-18.

67. Haque, R.; Freed, V.H. (1974) Behaviour of pesticides in the environment: Environmental chemodynamics. Residue Rev. 52:89-116.

68. Haseman J.K.; Huff, J.; Boorman, G.A. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

69. Haseman, J.K.; Huff, J.; Rao, G.N.; Arnold, J.; Boorman, G.A.; McConnell, E.E. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. J. Natl. Cancer Inst. 75:975-984.

70. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(Suppl. 1):3-142.

71. Heikes, D.L.; Griffitt, K.R. (1980) Pentachlorophenol in Mason jar lids and home canned food. J. Assoc. Off. Anal. Chem. 63:1125-1128.

72. Henry, R.J.; Chiamori, N.; Golub, O.J.; Berkman, S. (1960) Revised spectrophotometric methods for the determination of glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and lactic acid dehydrogenase. Am. J. Clin. Pathol. 34:381-398.

73. Henry, R.J.; Cannon, D.C.; Winkleman, J.W. (1974) Clinical Chemistry Principles and Techniques, 2nd ed. Hagerstown, MD: Harper & Row. 545 p.

74. Hirsch, A.A. (1942) Toxicity of sodium pentachlorophenate and other chemicals on water hyacinth. Bot. Gaz. 103:620-621.

75. Hoben, H.J.; Ching, S.A.; Casarett, L.J. (1976) A study of inhalation of pentachlorophenol by rats. III. Inhalation toxicity study. Bull. Environ. Contam. Toxicol. 15:463-465.

76. Holsapple, M.; McNerney, P.; Barnes, D.; White, K., Jr. (1984) Suppression of humoral antibody production by exposure to 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin. J. Pharmacol. Exp. Ther. 231:518-526.

77. Ingram, L.L.; McGinnis, G.D.; Gjovik, L.R. (1981) The relative amount of pentachlorophenol volatilization from treated wood. Proc. Am. Wood Preservers' Assoc. Annu. Meet., pp. 102-108.

78. Innes, J.R.M.; Ulland, B.M.; Valerio, M.G.; Petrucelli, L.; Fishbein, L.; Hart, E.R.; Pallotta, A.J.; Bates, R.R.; Falk, H.L.; Gart, J.J.; Klein, M.; Mitchell, I.; Peters, J. (1969) Bioassay of pesticides and industrial chemicals for tumourigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42:1101-1114.

79. International Programme on Chemical Safety (IPCS) (1987) Pentachlorophenol. Environmental Health Criteria 71. Geneva: World Health Organization, pp. 1-236.

80. International Register of Potentially Toxic Chemicals (IRPTC) (1983) Data Profile on Pentachlorophenol. Geneva, Switzerland: United Nations Environment Programme.

81. Jaffe, M. (1886) Uber den Niederschlag, welchen Pikrinsaure in normalem Harn erzeugt und uber eine neue Reaktion des Kreatinins. Z. Physiol. Chem. 10:391-400.

82. Jakobson, I.; Yllner, S. (1971) Metabolism of ^{14}C-pentachlorophenol in the mouse. Acta Pharmacol. Toxicol. 29:513-524.

83. Jansson, B.; Sundstrom, G.; Ahling, B. (1978) Formation of polychlorinated dibenzo-*p*-dioxins during combustion of chlorophenol formulations. Sci. Total Environ. 10:209-217.

84. Johnson, R.L.; Gehring, P.J.; Kociba, R.J.; Schwetz, B.A. (1973) Chlorinated dibenzodioxins and pentachlorophenol. Environ. Health Perspect. 5:171-175.

85. Jonckheere, A. (1954) A distribution-free k-sample test against ordered alternatives. Biometrika 41:133-145.

86. Jones, P.A. (1981) Chlorophenols and Their Impurities in the Canadian Environment. Report No. EPS 3-EC-81-2. Ottawa: Environment Canada. 434 p.

87. Kaplan, E.L.; Meier, P. (1958) Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. 53:457-481.

88. Karmen, A. (1955) A note on the spectrophotometric assay of glutamic oxalacetic transaminase in human blood serum. J. Clin. Invest. 34:131-133.

89. Kerkvliet, N.I.; Baecher-Steppan, L.; Claycomb, A.T.; Craig, A.M.; Sheggeby, G.G. (1982a) Immunotoxicity of technical pentachlorophenol (PCP-T): Depressed humoral immune response to T-dependent and T-independent antigen stimulation in PCP-T exposed mice. Fundam. Appl. Toxicol. 2:90-99.

90. Kerkvliet, N.I.; Baecher-Steppan, L.; Schmitz, J.A. (1982b) Immunotoxicity of pentachlorophenol (PCP): Increased susceptibility to tumour growth in adult mice fed technical PCP-contaminated diets. Toxicol. Appl. Pharmacol. 62:55-64.

91. Kerkvliet, N.; Brauner, J.; Matlock, J. (1985) Humoral immunotoxicity of polychlorinated diphenyl ethers, phenoxyphenols, dioxins and furans present as contaminants of technical grade pentachlorophenol. Toxicology 36:307-324.

92. Khera, K.S. (1974) Teratogenicity and dominant lethal studies on hexachlorobenzene in rats. Food Cosmet. Toxicol. 12:471-477.

93. Kimbrough, R.D. (1980) Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products. Amsterdam: Elsevier/North-Holland Biomedical Press. 406 p.

94. Kimbrough, R.D.; Linder, R.E. (1978) The effect of technical and purified pentachlorophenol on the rat liver. Toxicol. Appl. Pharmacol. 46:151-162.

95. Kinzell, J.H.; Ames, N.K.; Sleight, S.D.; Krehbiel, J.D.; Kuo, C.; Zabik, M.J.; Shull, L.R. (1981) Subchronic administration of technical pentachlorophenol to lactating dairy cattle: Performance, general health, and pathologic changes. J. Dairy Sci. 64:42-51.

96. Klemmer, H.W.; Wong, L.; Sato, M.M.; Reichert, E.L.; Korsak, R.J.; Rashad, M.N. (1980) Clinical findings in workers exposed to pentachlorophenol. Arch. Environ. Contam. Toxicol. 9:715-725.

97. Knudsen, I.; Verschuuren, H.G.; Den Tonkelaar, E.M.; Kroes, R.; Helleman, P.F.W. (1974) Short-term toxicity of pentachlorophenol in rats. Toxicology 2:141-152.

98. Kozak, V.P.; Simsiman, G.V.; Chesters, G.; Stensby, D.; Harkin, J. (1979) Reviews of the Environmental Effects of Pollutants: XI. Chlorophenols. USEPA Report No. 600/1-79-012. U.S. Environmental Protection Agency, Washington, DC. 492 p.

99. Krause, C. (1982) Active ingredients of wood preservatives used in homes. Aurand, K.; Seifert, B.; Wegner, J., Eds.: Air Quality in Interiors. Stuttgart: Gustav-Fischer-Verlag, pp. 309-316.

100. Kuhn, G.O.; Rollheiser, J.J.; Schworer, B.A.; Jameson, C.W. (1984) Methods development for mixing chemicals in rodent feed. Jameson, C.W.; Walters, D.B., Eds.: Chemistry for Toxicity Testing. Boston: Butterworth Publishers.

101. Larsen, R.V.; Kirsch, L.E.; Shaw, S.M.; Christian, J.E.; Born, G.S. (1972) Excretion and tissue distribution of uniformly labelled ^{14}C-pentachlorophenol in rats. J. Pharm. Sci. 61:2004-2006.

102. Lillie, R.D.; Fullmer, H.M. (1968) Histopathologic Technique and Practical Histochemistry, 4th ed. New York: McGraw-Hill, p. 317.

103. Linhart, M.S.; Cooper, J.; Martin, R.L.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comput. Biomed. Res. 7:230-248.

104. Lowry, O.H.; Rosebrough, N.J.; Farr, A.L.; Randall, R.J. (1951) Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193:265-275.

105. Luna, L.G. (1968) Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology, 3rd ed. New York: McGraw-Hill, pp. 141, 220.

106. Luster, M.; Blank, J.; Dean, J. (1987) Molecular and cellular basis of chemically induced immunotoxicity. Annu. Rev. Pharmacol. Toxicol. 27:23-49.

107. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

108. Maronpot, R.R.; Boorman, G.A. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

109. McConnell, E.E. (1980) Acute and chronic toxicity, carcinogenesis, reproduction, teratogenesis and mutagenesis in animals. Kimbrough, R.D., Ed.: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 151-190.

110. McConnell, E.E. (1983a) Pathology requirements for rodent two-year studies. I. A review of current procedures. Toxicol. Pathol. 11:60-64.

111. McConnell, E.E. (1983b) Pathology requirements for rodent two-year studies. II. Alternative approaches. Toxicol. Pathol. 11:65-76.

112. McConnell, E.E. (1984) Clinicopathologic concepts of dibenzo-p-dioxin intoxication. Poland, A.; Kimbrough, R.D., Eds.: Banbury Report 18 - Biological Mechanisms of Dioxin Action. Long Island, NY: Cold Spring Harbor Laboratory, pp. 27-37.

113. McConnell, E.E.; Moore, J.A.; Haseman, J.K.; Harris, M.W. (1978) The comparative toxicity of chlorinated dibenzo-*p*-dioxins in mice and guinea-pigs. Toxicol. Appl. Pharmacol. 44:335-356.

114. McConnell, E.E.; Moore, J.A.; Gupta, B.N.; Rakes, A.H.; Luster, M.I.; Goldstein, J.A.; Haseman, J.K.; Parker, C.E. (1980) The chronic toxicity of technical and analytical pentachlorophenol in cattle. I. Clinicopathology. Toxicol. Appl. Pharmacol. 52:468-490.

V. REFERENCES

115. McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

116. McKnight, B.; Crowley, J. (1984) Tests for differences in tumor incidence based on animal carcinogenesis experiments. J. Am. Stat. Assoc. 79:639-648.

117. Mercier, M. (1981) Criteria (Dose/Effect Relationships) for Organochlorine Pesticides. Oxford: Pergamon Press. 381 p.

118. The Merck Index (1976) 9th ed. Rahway, NJ: Merck & Co., Inc., p. 921.

119. Meyer, O.A.; Tilson, H.A.; Byrd, W.C.; Riley, M.T. (1979) A method for the routine assessment of fore- and hindlimb grip strength of rats and mice. Neurobehav. Toxicol. 1:233-236.

120. Miller, J.A.; Miller, E.C. (1977) Ultimate chemical carcinogens as reactive mutagenic electrophiles. Hiatt, H.H.; Watson, J.D.; Winsten, J.A., Eds.: Origins of Human Cancer (Book B). Long Island, NY: Cold Spring Harbor Laboratory, pp. 605-628.

121. Moore, J.A.; McConnell, E.E.; Dalgard, D.W.; Harris, M.W. (1979) Comparative toxicity of three halogenated dibenzofurans in guinea pigs, mice, and rhesus monkeys. Ann. N.Y. Acad. Sci. 320:151-163.

122. Moriya, M.; Ohta, T.; Watanabe, K.; Miyazawa, T.; Kato, K.; Shirasu, Y. (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116:185-216.

123. Mortelmans, K.; Haworth, S.; Lawlor, T.; Speck, W.; Tainer, B.; Zeiger, E. (1986) Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. Environ. Mutagen. 8(Suppl. 7):1-119.

124. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 65 p.

125. National Cancer Institute (NCI) (1980) Bioassay of a Mixture of 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Gavage) for Possible Carcinogenicity. NCI Technical Report No. 198. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 173 p.

126. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

127. National Research Council of Canada (NRCC) (1982) Chlorinated Phenols: Criteria for Environmental Quality. NRCC Report No. 18578. Associate Committee on Scientific Criteria for Environmental Quality, Ottawa, Ontario. 191 p.

128. National Toxicology Program (NTP) (1982) Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Osborne-Mendel Rats and B6C3F_1 Mice (Gavage Study). NTP Technical Report No. 209. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 195 p.

129. National Toxicology Program (NTP) (1984) Report of the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation. Research Triangle Park, NC: NTP, p. 280.

130. Nishimura, N.; Nishimura, H.; Oshima, H. (1982) Survey on mutagenicity of pesticides by the *Salmonella*-microsome test. Aichi Ika Daigaku Igakukai Zasshi 10:305-312.

131. Omura, T.; Sato, R. (1964) The carbon monoxide-binding pigment of liver microsomes I. Evidence for its hemoprotein nature. J. Biol. Chem. 239:2370-2379.

132. Osterloh, J.; Letz, G.; Pond, S.; Becker, C. (1983) An assessment of the potential testicular toxicity of 10 pesticides using the mouse-sperm morphology assay. Mutat. Res. 116:407-415.

133. Parker, C.E.; Jones, W.A.; Matthews, H.B.; McConnell, E.E.; Hass, J.R. (1980) The chronic toxicity of technical and analytical pentachlorophenol in cattle. II. Chemical analyses of tissues. Toxicol. Appl. Pharmacol. 55:359-369.

134. Petrowitz, H.J. (1981) Volatilisation of the Active Ingredients of Wood Preservatives from Chemically Protected Timber. Research Report of the Expert Group on Biological Materials Research. Federal Institute for Materials Research, Berlin. 32 p.

135. Pitot, H.C.; Goldsworthy, T.; Campbell, H.A.; Poland, A. (1980) Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res. 40:3616-3620.

136. Poland, A.; Kimbrough, R.D. (1984) Banbury Report 18 - Biological Mechanisms of Dioxin Action. Long Island, NY: Cold Spring Harbor Laboratory. 500 p.

137. Ramel, C.; Magnusson, J. (1979) Chemical induction of nondisjunction in Drosophila. Environ. Health Perspect. 31:59-66.

138. Renner, G.; Hopfer, C.; Gokel, J.M. (1986) Acute toxicities of pentachlorophenol, pentachloroanisole, tetrachlorohydroquinone, tetrachlorocatechol, tetrachlororesorcinol, and tetrachlorodimethoxybenzene diacetates administered to mice. Toxicol. Environ. Chem. 11:37-50.

139. Rosskamp, E. (1982) Pentachlorophenol as a Model Case of a Xenobiotic Compound: PCP in the Environment. Research Report No. 10604007. Berlin: Federal Health Office Institute for Water, Soil and Air Hygiene. 22 p.

140. Rott, B.; Nitz, S.; Korte, F. (1979) Microbial decomposition of sodium pentachlorophenolate. J. Agric. Food Chem. 27:306-310.

141. Ryan, J.J. (1983) Higher chlorinated dioxins implicated in the mortality of young pigs kept on a pentachlorophenol-treated wooden floor. Can. Vet. J. 24:72-75.

142. Sadtler Standard Spectra, IR No. 279. Philadelphia: Sadtler Research Laboratories.

143. Safe, S. (1980) Metabolism, uptake, storage and bioaccumulation. Kimbrough, R.D., Ed.: Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Compounds. Amsterdam: Elsevier/North-Holland Biomedical Press, pp. 81-108.

144. Samoiloff, M.R.; Schulz, S.; Jordan, Y.; Denich, K.; Arnott, E. (1980) A rapid simple long-term toxicity assay for aquatic contaminants using the nematode *Panagrellus redivivus*. Can. J. Fish Aquatic Sci. 37:1167-1174.

145. Saur, J.M.; Walcheski, P.J.; Nicholas, D.-D.; Gjovik, L.R. (1982) The concentration of airborne pentachlorophenol within treated wood structures. Proc. Am. Wood Preservers' Assoc. Annu. Meet., pp. 169-173.

146. Schwetz, B.A.; Keeler, P.A.; Gehring, P.J. (1974) The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol. Appl. Pharmacol. 28:151-161.

147. Schwetz, B.A.; Quast, I.F.; Keeler, P.A.; Humiston, C.G.; Kociba, R.J. (1978) Results of two-year toxicity and reproduction studies on pentachlorophenol in rats. Rao, K.R., Ed.: Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology. New York: Plenum Press, pp. 301-309.

148. Sheehan, D.C.; Hrapchak, B.B. (1980) Theory and Practice of Histotechnology, 2nd ed. St. Louis: C.V. Mosby Co., pp. 166, 218, 220.

149. Shirasu, Y. (1975) Significance of mutagenicity testing on pesticides. Environ. Qual. Saf. 4:226-231.

150. Shirley, E. (1977) A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. Biometrics 7:386-389.

151. Sikka, K.; Sharma, A.K. (1976) The effects of some herbicides on plant chromosomes. Proc. Indian Natl. Sci. Acad. 42(Part B):299-307.

152. Simmon, V.F.; Kauhanen, K. (1978) *In vitro* Microbiological Mutagenicity Assays of Pentachlorophenol. Final Report. SRI Project LSU-5612. U.S. Environmental Protection Agency, National Environmental Research Center, Cincinnati, OH. 13 p.

153. Simon, G.S.; Tardiff, R.G.; Borzelleca, J.F. (1979) Failure of hexachlorobenzene to induce dominant lethal mutations in the rat. Toxicol. Appl. Pharmacol. 47·415-419.

154. Slot, C. (1965) Plasma creatinine determination. A new and specific Jaffe reaction method. Scand. J. Clin. Lab. Invest. 17:381-387.

155. Stockdale, M.; Selwyn, M.J. (1971a) Influence of ring substituents on the action of phenols on some dehydrogenases, phosphokinases, and the soluble ATPase from mitochondria. Eur. J. Biochem. 21:416-423.

156. Stockdale, M.; Selwyn, M.J. (1971b) Effects of ring substituents on the activity of phenols as inhibitors and uncouplers of mitochondrial respiration. Eur. J. Biochem. 21:565-574.

157. Swenberg, J.A.; Barrow, C.S.; Boreiko, C.J.; Heck, H.d'A.; Levine, R.J.; Morgan, K.T.; Starr, T.B. (1983) Non-linear biological responses to formaldehyde and their implications for carcinogenic risk assessment. Carcinogenesis 4:945-952.

158. Szasz, G. (1969) Kinetic photometric method for serum γ-glutamyl transpeptidase. Clin. Chem. 15:124-136.

159. Tarone, R.E. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

160. Thompson, G.E.; Husain, H.; Parry, J.; Wardrop, W.L; Gilbride, P.J. (1978) Hydrogeological control and clean-up of soil and groundwater contaminants at Northern Wood Preservers, Ltd. Proc. Ontario Industrial Waste Conference, June 18-21. Winnipeg, Manitoba: Engineering Consultants. 18 p.

161. Trevors, J.T. (1982) Effect of temperature on the degradation of pentachlorophenol by *Pseudomonas* spp. Chemosphere 11:471-475.

162. Uhl, S.; Schmid, P.; Schlatter, C. (1986) Pharmacokinetics of pentachlorophenol in man. Arch. Toxicol. 58:182-186.

163. U.S. Environmental Protection Agency (USEPA) (1979) Reviews of the Environmental Effects of Pollutants: XI. Chlorophenols. HERL, ORD, Cincinnati, OH.

164. Vogel, E.; Chandler, J.L.R. (1974) Mutagenicity testing of cyclamate and some pesticides in *Drosophila melanogaster*. Experientia 30:621-623.

165. Wainstock de Calmanovici, R.; San Martin de Viale, L.C. (1980) Effect of chlorophenols on porphyrin metabolism in rats and chick embryo. Int. J. Biochem. 12:1039-1044.

166. Watanabe, I. (1973) Isolation of pentachlorophenol decomposing bacteria from soil. Soil Sci. Plant Nutr. 19:109-116.

167. Welsh, J.J.; Collins, T.F.X.; Black, T.N.; Graham, S.L.; O'Donnell, M.W., Jr. (1987) Teratogenic potential of purified pentachlorophenol and pentachloroanisole in subchronically exposed Sprague-Dawley rats. Food Chem. Toxicol. 25:163-172.

168. Wilkinson, J.H.; Boutwell, J.H.; Winsten, S. (1969) Evaluation of a new system for the kinetic measurement of serum alkline phosphatase. Clin. Chem. 15:487-495.

169 Wong, A S , Crosby, D G (1981) Photodecomposition of pentachlorophenol in water J Agric Food Chem 29(No 2) 125-130

170 Wroblewski, F , LaDue, J S (1956) Serum glutamic-pyruvic transaminase in cardiac and hepatic disease Proc Soc Exp. Biol Med 91 569-571

171 Young, A L , Calcagin, J A , Tremblay, J W (1978) The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and Its Associated Dioxin U S Air Force Technical Report OEHL TR 78-79 Aerospace Medical Division (AFSC), Brooks Air Force Base, TX

172 Zeiger, E , Anderson, B , Haworth, S , Lawlor, T , Mortelmans, K , Speck, W (1987) Salmonella mutagenicity tests III Results from the testing of 255 chemicals Environ Mutagen. 9(Suppl 9) 1-110

173 Zeiger, E , Anderson, B , Haworth, S , Lawlor, T , Mortelmans, K (1988) *Salmonella* mutagenicity tests IV Results from the testing of 300 chemicals Environ Molec Mutagen. 11(Suppl 12) 1-158

174 Zimmerli, B (1982) Modelling the transfer of pollutants from painted surfaces in the surrounding air Aurand, K , Seifert, B , Wegner, J , Eds Air quality in closed rooms Stuttgart. Gustav Fischer Verlag, pp. 235-267

APPENDIX A

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	35	50	50
Animals removed	35	50	50
Animals examined histopathologically	35	49	49
ALIMENTARY SYSTEM			
Gallbladder	(20)	*(49)	(32)
Lymphoma malignant mixed			1 (3%)
Intestine small, duodenum	(24)	*(49)	(38)
Polyp adenomatous	1 (4%)		
Intestine small, jejunum	(26)	*(49)	(37)
Lymphoma malignant mixed			1 (3%)
Liver	(32)	(47)	(48)
Cholangiocarcinoma		1 (2%)	
Hemangioma			1 (2%)
Hemangiosarcoma		1 (2%)	1 (2%)
Hemangiosarcoma, multiple		1 (2%)	
Hepatocellular carcinoma	1 (3%)	9 (19%)	11 (23%)
Hepatocellular carcinoma, multiple	1 (3%)	1 (2%)	1 (2%)
Hepatocellular adenoma	5 (16%)	12 (26%)	15 (31%)
Hepatocellular adenoma, multiple		8 (17%)	18 (38%)
Hepatocholangiocarcinoma			1 (2%)
Lymphoma malignant histiocytic		1 (2%)	1 (2%)
Lymphoma malignant mixed	1 (3%)		2 (4%)
Sarcoma, metastatic, skin			1 (2%)
Mesentery	*(35)	*(49)	*(49)
Fibrosarcoma, metastatic, skin	1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)
Pancreas	(27)	*(49)	(44)
Fibrosarcoma, metastatic, skin	1 (4%)		
Stomach, forestomach	(31)	*(49)	(43)
Papilloma squamous			1 (2%)
Tooth	*(35)	*(49)	*(49)
Periodontal tissue, sarcoma	1 (3%)		
CARDIOVASCULAR SYSTEM			
Heart	(33)	*(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(31)	(47)	(46)
Capsule, adenoma		1 (2%)	
Capsule, fibrosarcoma, metastatic, skin	1 (3%)		
Capsule, sarcoma, metastatic, skin	1 (3%)		
Adrenal gland, medulla	(31)	(45)	(45)
Pheochromocytoma benign		4 (9%)	4 (9%)
Bilateral, pheochromocytoma benign		6 (13%)	19 (42%)
Thyroid gland	(31)	*(49)	(47)
Follicular cell, adenoma	1 (3%)		1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Preputial gland	*(35)	*(49)	*(49)
Carcinoma		1 (2%)	1 (2%)
Prostate	(34)	*(49)	(45)
Lymphoma malignant mixed			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node	(27)	*(49)	(44)
Axillary, lymphoma malignant histiocytic			1 (2%)
Axillary, inguinal, fibrosarcoma, metastatic, skin	1 (4%)		
Inguinal, lymphoma malignant histiocytic			1 (2%)
Inguinal, sarcoma, metastatic, skin			1 (2%)
Lumbar, lymphoma malignant histiocytic		1 (2%)	1 (2%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Mediastinal, lymphoma malignant histiocytic		1 (2%)	
Mediastinal, lymphoma malignant mixed			1 (2%)
Mesenteric, lymphoma malignant histiocytic		1 (2%)	1 (2%)
Mesenteric, lymphoma malignant lymphocytic			1 (2%)
Mesenteric, lymphoma malignant mixed	1 (4%)	1 (2%)	2 (5%)
Pancreatic, lymphoma malignant histiocytic		1 (2%)	
Renal, lymphoma malignant histiocytic			1 (2%)
Lymph node, mandibular	(27)	*(49)	(43)
Lymphoma malignant histiocytic		1 (2%)	1 (2%)
Lymphoma malignant mixed			2 (5%)
Spleen	(30)	*(49)	(46)
Hemangioma			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (3%)		1 (2%)
INTEGUMENTARY SYSTEM			
Skin	(33)	*(49)	(49)
Basosquamous tumor malignant		1 (2%)	
Carcinoma		1 (2%)	
Squamous cell carcinoma			1 (2%)
Subcutaneous tissue, fibroma		2 (4%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	1 (3%)	9 (18%)	3 (6%)
Subcutaneous tissue, fibrosarcoma, multiple	1 (3%)	1 (2%)	
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver			1 (2%)
Subcutaneous tissue, mast cell tumor benign	1 (3%)		
Subcutaneous tissue, sarcoma	2 (6%)		4 (8%)
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(33)	*(49)	(49)
Alveolar/bronchiolar adenoma	2 (6%)	1 (2%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	
Fibrosarcoma, metastatic, skin		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (3%)		1 (2%)
Lymphoma malignant mixed			1 (2%)
Sarcoma, metastatic, skin	1 (3%)		2 (4%)
Sarcoma, metastatic, tooth	1 (3%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Harderian gland	*(35)	*(49)	*(49)
Adenoma	1 (3%)		2 (4%)
URINARY SYSTEM			
Kidney	(33)	*(49)	(47)
Fibrosarcoma, metastatic, skin	1 (3%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)
Lymphoma malignant mixed			2 (4%)
Urinary bladder	(34)	*(49)	(43)
Hemangioma	1 (3%)		
SYSTEMIC LESIONS			
Multiple organs	*(35)	*(49)	*(49)
Hemangioma	1 (3%)		2 (4%)
Lymphoma malignant mixed	1 (3%)	1 (2%)	2 (4%)
Hemangiosarcoma		2 (4%)	1 (2%)
Lymphoma malignant histiocytic		1 (2%)	2 (4%)
Lymphoma malignant lymphocytic			2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	35	50	50
Terminal sacrifice	12	24	22
Natural death	18	14	21
Moribund sacrifice	5	12	3
Drowned			4
TUMOR SUMMARY			
Total animals with primary neoplasms **	17	38	45
Total primary neoplasms	20	63	100
Total animals with benign neoplasms	11	28	38
Total benign neoplasms	12	34	71
Total animals with malignant neoplasms	8	27	26
Total malignant neoplasms	8	29	29
Total animals with secondary neoplasms ***	5	2	4
Total secondary neoplasms	9	2	10

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	015	018	027	038	041	048	050	052	060	061	061	061	068	072	073	078	078	079	086	087	097	097	097	105	105
CARCASS ID	1711	1011	0711	2311	2011	1511	2411	2111	1211	0911	0611	3111	2211	0411	3211	3011	2611	1811	1611	3311	3411	2711	1111	0311	0511
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Gallbladder	A	A	M	A	A	+	M	+	A	+	+	A	+	A	A	+	+	A	A	A	+	+	A	+	+
Intestine large	+	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Intestine large, cecum	M	A	A	A	A	+	A	+	+	+	M	A	+	+	A	+	+	A	A	+	+	+	+	+	+
Intestine large, colon	A	+	A	A	A	+	A	+	+	+	+	+	+	+	M	+	+	A	A	+	+	+	+	+	+
Intestine large, rectum	M	A	A	A	A	+	A	+	+	+	+	A	+	+	M	+	+	A	A	+	+	+	+	+	+
Intestine small	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	A	A	+	M	+	+	+	M	A	+	+	A	+	+	A	A	+	+	+	+	+	+
Polyp adenomatous																					X				
Intestine small, ileum	M	A	A	A	A	M	A	+	+	+	M	A	+	+	M	+	+	A	A	+	+	+	+	+	+
Intestine small, jejunum	M	A	A	A	A	+	A	+	+	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+
Liver	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Hepatocellular carcinoma, multiple														X											
Hepatocellular adenoma						X			X												X				
Lymphoma malignant mixed																									
Mesentery								+													+				
Fibrosarcoma, metastatic, skin																					X				
Pancreas	M	+	A	M	A	+	M	+	+	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																					X				
Salivary glands	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Stomach	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Tooth												+													
Peridontal tissue, sarcoma												X													
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Capsule, fibrosarcoma, metastatic, skin																					X				
Capsule, sarcoma, metastatic, skin																				X					
Adrenal gland, cortex	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Adrenal gland, medulla	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Islets, pancreatic	M	+	A	A	A	+	M	+	+	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	+	M	M	+	I	+	M	+	+	+	+	M	M	A	+	+	+	+	+	+
Pituitary gland	A	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+
Thyroid gland	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Follicular cell, adenoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Penis							+	+																	
Preputial gland						+	+	+						+	+								+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Seminal vesicle									+	+						+	+						+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+

\+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (*Continued*)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	1311	1411	1911	2511	0111	0211	0811	2811	2911	3511	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	32
Gallbladder	+	+	+	+	+	+	+	+	M	+	20
Intestine large	+	+	+	+	+	+	+	+	+	+	29
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	24
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	27
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	25
Intestine small	+	+	+	+	+	+	+	+	+	+	29
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	24
Polyp adenomatous											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	23
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	26
Liver	+	+	+	+	+	+	+	+	+	+	32
Hepatocellular carcinoma											1
Hepatocellular carcinoma, multiple											1
Hepatocellular adenoma		X				X					5
Lymphoma malignant mixed	X										1
Mesentery											2
Fibrosarcoma, metastatic, skin											1
Pancreas	+	+	+	+	+	+	+	+	+	+	27
Fibrosarcoma, metastatic, skin											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	32
Stomach	+	+	+	+	+	+	+	+	+	+	31
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	31
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	31
Tooth											1
Peridontal tissue, sarcoma											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	33
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	31
Capsule, fibrosarcoma, metastatic, skin											1
Capsule, sarcoma, metastatic, skin											1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	31
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	31
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	27
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	24
Pituitary gland	+	+	+	+	+	+	+	+	+	+	29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	31
Follicular cell, adenoma											1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	34
Penis											2
Preputial gland											6
Prostate	+	+	+	+	+	+	+	+	+	+	34
Seminal vesicle	+		+								7
Testes	+	+	+	+	+	+	+	+	+	+	34

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	015	018	027	038	041	048	050	052	060	061	061	061	068	072	073	078	078	079	086	087	097	097	097	105	105
CARCASS ID	171	101	071	231	201	151	241	211	121	091	061	311	221	041	321	301	261	181	161	331	341	271	111	031	051
HEMATOPOIETIC SYSTEM																									
Blood																	+			+					
Bone marrow	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+
Lymph node	M	M	+	M	A	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	M	+	+	+
Axillary, inguinal, fibrosarcoma, metastatic, skin																									
Mesenteric, lymphoma malignant mixed																									
Lymph node, mandibular	M	M	+	M	A	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	M	+	+	+
Spleen	M	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+
Lymphoma malignant mixed																									
Thymus	M	+	M	M	M	+	M	M	+	+	+		+	M	M	+	+	M	M	M	M	M	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																					X				
Subcutaneous tissue, fibrosarcoma, multiple																									
Subcutaneous tissue, mast cell tumor benign																	X								
Subcutaneous tissue, sarcoma																		X		X					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic, liver														X											
Sarcoma, metastatic, tooth													X												
Sarcoma, metastatic, skin																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+											+													
Harderian gland	+	+	M	M	+	+	A	+	+	+	M	+	+	+	+	M	+	+	A	+	+	+	+	+	+
Adenoma																		X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																					X				
Urethra	+				+		+	+	+						+										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hemangioma										X															

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL.
CARCASS ID	1 3 1	1 4 1	1 9 1	2 5 1	0 1 1	0 2 1	0 8 1	2 8 1	2 9 1	3 5 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM											
Blood											2
Bone marrow	+	+	+	+	+	+	+	+	+	+	30
Lymph node	+	+	+	+	+	+	+	+	+	+	27
Axillary, inguinal, fibrosarcoma, metastatic, skin									X		1
Mesenteric, lymphoma malignant mixed	X										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	27
Spleen	+	+	+	+	+	+	+	+	+	+	30
Lymphoma malignant mixed	X										1
Thymus	M	M	+	+	+	+	M	+	M	+	16
INTEGUMENTARY SYSTEM											
Mammary gland	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	33
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, fibrosarcoma, multiple									X		1
Subcutaneous tissue, mast cell tumor benign											1
Subcutaneous tissue, sarcoma											2
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	35
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	31
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	33
Alveolar/bronchiolar adenoma				X			X				2
Hepatocellular carcinoma, metastatic, liver											1
Sarcoma, metastatic, tooth											1
Sarcoma, metastatic, skin											1
Nose	+	+	+	+	+	+	+	+	+	+	35
Trachea	+	+	+	+	+	+	+	+	+	+	31
SPECIAL SENSES SYSTEM											
Eye											2
Harderian gland	+	+	+	+	+	+	+	+	+	+	29
Adenoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	33
Fibrosarcoma, metastatic, skin											1
Urethra											6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	34
Hemangioma											1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	027	045	048	050	055	059	071	075	077	078	078	080	083	084	090	090	091	091	094	095	098	099	099	101	101
CARCASS ID	861	651	851	671	471	681	701	641	531	801	781	511	661	481	771	461	821	431	841	571	721	691	911	711	501
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Gallbladder	A	A	+	A	A	+	A	A	+	A	+	+	+	+	+	A	A								
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Intestine large, cecum	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+								
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Intestine large, rectum	A	A	+	+	A	+	+	+	+	+	+	+	+	M	+	A	+								
Intestine small	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+								
Intestine small, duodenum	A	A	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+								
Intestine small, ileum	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+								
Intestine small, jejunum	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+								
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+		+	+	+	+	+	+	+
Cholangiocarcinoma																				X					
Hemangiosarcoma																									
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma								X													X				X
Hepatocellular carcinoma, multiple																			X						
Hepatocellular adenoma						X							X	X						X			X		
Hepatocellular adenoma, multiple																			X						
Lymphoma malignant histiocytic											X														
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Salivary glands	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Stomach	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+								
Stomach, forestomach	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+								
Stomach, glandular	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+								
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
ENDOCRINE SYSTEM																									
Adrenal gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+		+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	A	+	+	+	+	+	+	+		+	+	+	+	+	A	+		+	+	+	+	+	+	+
Adrenal gland, medulla	+	A	+	+	+	+	+	+	+		+	+	+	+	+	A	+		+	+	+	+	+	+	+
Pheochromocytoma benign																									X
Bilateral, pheochromocytoma benign																					X				
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Parathyroid gland	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	A	M								
Pituitary gland	M	A	+	+	+	I	+	+	M	+	+	+	+	+	+	M	+								
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Penis	+				+	+															+		+		
Preputial gland			+		+								+						+				+		
Carcinoma																									
Prostate	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Seminal vesicle		+		+		+		+																	
Testes	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	551	441	451	541	561	741	751	891	901	921	521	581	611	631	791	881	491	591	601	621	731	761	811	831	871	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										17
Gallbladder																										8
Intestine large																										15
Intestine large, cecum																										12
Intestine large, colon																										15
Intestine large, rectum																										12
Intestine small																										13
Intestine small, duodenum																										12
Intestine small, ileum																										13
Intestine small, jejunum																										13
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Cholangiocarcinoma																										1
Hemangiosarcoma							X																			1
Hemangiosarcoma, multiple												X														1
Hepatocellular carcinoma	X		X	X												X			X		X					9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma			X		X						X								X				X	X	X	12
Hepatocellular adenoma, multiple						X	X	X	X				X				X				X					8
Lymphoma malignant histiocytic																										1
Pancreas																										15
Salivary glands																										15
Stomach																										14
Stomach, forestomach																										14
Stomach, glandular																										14
CARDIOVASCULAR SYSTEM																										
Heart	+																									18
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Capsule, adenoma																	X									1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*I*	+	+		45
Pheochromocytoma benign	X				X															X						4
Bilateral, pheochromocytoma benign				X										X	X	X					X					6
Islets, pancreatic																										15
Parathyroid gland																										12
Pituitary gland																										12
Thyroid gland																										15
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																	+									17
Penis																										5
Preputial gland						+																				6
Carcinoma						X																				1
Prostate																										15
Seminal vesicle																										4
Testes																									+	17

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	027	045	048	050	050	059	071	075	077	078	078	080	083	084	090	090	091	091	094	095	098	099	099	101	101
CARCASS ID	861	651	851	671	471	681	701	641	531	801	781	511	661	481	771	461	821	431	841	571	721	691	911	711	501
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
Lymph node	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+								
Lumbar, lymphoma malignant histiocytic											X														
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung										X															
Mediastinal, lymphoma malignant histiocytic											X														
Mesenteric, lymphoma malignant histiocytic											X														
Mesenteric, lymphoma malignant mixed																									
Pancreatic, lymphoma malignant histiocytic											X														
Lymph node, mandibular	+	M		+	M	+	+	+	+		+	+	+	+	+	A	+								
Lymphoma malignant histiocytic											X														
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+				+	+		+	
Thymus	+	A	+	M	+	+	M	M	M	M	+	M	+	+	I	M	I								
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M								
Skin	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	A	+		+			+	+	+	
Basosquamous tumor malignant																	X								
Carcinoma												X													
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma								X	X						X									X	
Subcutaneous tissue, fibrosarcoma, multiple																						X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+				+	+
Skeletal muscle												+													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma										X															
Fibrosarcoma, metastatic, skin									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
SPECIAL SENSES SYSTEM																									
Harderian gland	M	+	M		+	+	+	+	+	+	+	+	+	M	+	M	+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+								+
Urethra	+					+																			
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+						+		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	55 1	44 1	45 1	54 1	56 1	74 1	75 1	89 1	90 1	92 1	52 1	58 1	81 1	63 1	79 1	88 1	49 1	59 1	60 1	62 1	73 1	76 1	81 1	83 1	87 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood									+																	1
Bone marrow																										15
Lymph node	+					+		+	+	+	+					+	+	+			+					24
Lumbar, lymphoma malig histiocytic																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant mixed								X																		1
Pancreatic, lymphoma malignant histiocytic																										1
Lymph node, mandibular																										12
Lymphoma malignant histiocytic																										1
Spleen			+						+		+	+												+		23
Thymus																										7
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin			+						+		+			+			+			+				+	+	27
Basosquamous tumor malignant																										1
Carcinoma																										1
Subcutaneous tissue, fibroma																				X						2
Subcutaneous tissue, fibrosarcoma			X						X		X						X								X	9
Subcutaneous tissue, fibrosarcoma, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone						I	+				+	+	+	+				+		+	+					28
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain																										16
RESPIRATORY SYSTEM																										
Lung														+												18
Alveolar/bronchiolar adenoma														X												1
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										1
Nose																										17
Trachea																										17
SPECIAL SENSES SYSTEM																										
Harderian gland																										12
URINARY SYSTEM																										
Kidney																								+		18
Urethra																										2
Urinary bladder																										15

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	021	043	054	054	054	054	064	068	070	074	076	078	079	082	084	084	085	086	089	091	092	092	094	094	098
CARCASS ID	11501	11901	11801	12001	12101	12201	13701	14501	10901	14001	10801	12301	13301	11701	11201	11301	10601	13501	14701	15001	13001	14601	14401	11001	10501
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
Gallbladder	+	A	+	+	+	+	A	A	A	A	M	+	+	A	A	A	A	A	A		+	+	A	A	A
Lymphoma malignant mixed																									
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	A	A		+	+	+	+	+
Intestine large, cecum	+	M	+	+	+	+	+	A	A	A	A	+	+	A	M	A	A	A	A		+	+	+	M	+
Intestine large, colon	+	A	+	+	+	+	+	A	+	+	A	+	+	A	+	A	+	A	A		+	+	+	A	+
Intestine large, rectum	+	M	+	+	+	+	+	A	A	M	M	+	+	M	A	A	A	A	A		+	+	+	A	+
Intestine small	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	A	A		+	+	+	M	+
Intestine small, duodenum	M	A	+	+	+	+	+	A	A	A	A	+	+	+	M	+	A	A	A		+	+	+	M	+
Intestine small, ileum	+	M	+	+	+	+	+	A	A	M	A	+	+	A	A	A	A	A	A		+	+	+	M	+
Intestine small, jejunum	+	A	+	+	+	+	+	A	A	A	A	+	+	A	A	A	A	A	A		+	+	+	M	+
Lymphoma malignant mixed																					X				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
Hemangioma															X										
Hemangiosarcoma																									
Hepatocellular carcinoma										X	X		X	X									X		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma			X	X	X			X				X			X		X	X					X	X	X
Hepatocellular adenoma, multiple									X							X									
Hepatocholangiocarcinoma																									X
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																					X				
Sarcoma, metastatic, skin							X																		
Mesentery			+																						+
Hepatocholangiocarcinoma, metastatic, liver																									X
Pancreas	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	A	A		+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
Stomach	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	A	A	+	M	+	+	+	+	+	+	A	A		+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	A		+	+	+	A	+
Tooth																					+				
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									X
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Adrenal gland, medulla	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Pheochromocytoma benign													X												
Bilateral, pheochromocytoma benign																						X	X		
Islets, pancreatic	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	A	A		+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	M	M	+	M	+	+	+	+	M	+	+	M		+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	M	M	A	M		M	+	+	+	+
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
Penis		M																							
Preputial gland			+		+	+																+			
Carcinoma																									
Prostate	+	M	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	A		+	+	+	+	+
Lymphoma malignant mixed																					X				
Seminal vesicle		+						+	+					+							+	+			
Testes	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	0 9 9	1 0 1	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	1 3 8 1	1 1 1	1 0 3 1	1 0 4 1	1 0 7 1	1 2 7 1	1 3 1 1	1 4 1 1	1 4 3 1	1 4 9 1	1 5 1 1	1 1 6 1	1 2 4 1	1 2 6 1	1 2 8 1	1 2 9 1	1 3 4 1	1 4 2 1	1 5 2 1	1 1 4 1	1 2 5 1	1 3 2 1	1 3 6 1	1 3 9 1	1 4 8 1	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Lymphoma malignant mixed				X																						1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, rectum	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																										1
Hemangiosarcoma																									X	1
Hepatocellular carcinoma			X		X			X							X	X							X			11
Hepatocellular carcinoma, multiple																						X				1
Hepatocellular adenoma		X				X	X	X																		15
Hepatocellular adenoma, multiple			X	X	X					X	X	X	X		X	X	X		X	X	X	X	X	X		18
Hepatocholangiocarcinoma																										1
Lymphoma malignant histiocytic	X																									1
Lymphoma malignant mixed				X																						2
Sarcoma, metastatic, skin																										1
Mesentery																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Papilloma squamous							X																			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	42
Tooth												+								+						3
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pheochromocytoma benign							X				X							X								4
Bilateral, pheochromocytoma benign		X	X	X	X			X	X			X	X	X	X	X	X			X	X	X	X	X		19
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell, adenoma																X										1
GENERAL BODY SYSTEM																										
Tissue, NOS								+																		1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Penis																										
Preputial gland			+												+								+	+		8
Carcinoma															X											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant mixed																										1
Seminal vesicle																				+						7
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	021	043	054	054	054	054	064	068	070	074	076	078	079	082	084	084	085	086	089	091	092	092	094	094	098
CARCASS ID	11551	11991	11981	12201	12211	12221	13711	14511	14091	14401	14081	12331	13331	11771	11121	11131	10661	13551	14711	15011	13301	14461	14441	14101	10551
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M		+	+	+	+	+
Axillary, lymphoma malignant histiocytic																									
Inguinal, lymphoma malignant histiocytic																									
Inguinal, sarcoma, metastatic, skin							X																		
Lumbar, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant histiocytic																									
Mesenteric, lymphoma malignant lymphocytic																									
Mesenteric, lymphoma malignant mixed																					X				
Renal, lymphoma malignant histiocytic																									
Lymph node, mandibular	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M		+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																					X				
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	A		+	+	+	+	+
Hemangioma																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Thymus	M	M	+	+	+	+	M	M	M	+	M	M	M	M	M	M	M	M	M		M	M	M	M	M
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver																									X
Subcutaneous tissue, sarcoma							X					X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant mixed																									
Sarcoma, metastatic, skin							X					X													
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye																									
Harderian gland	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A		+	+	-	+	+
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A		+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									X
Lymphoma malignant mixed																					X				
Urinary bladder	+	A	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	A	A		+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	099	101	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	13381	11111	10311	10441	10071	12711	13111	14111	14431	14491	15111	11161	12441	12661	12881	12991	13411	14211	15211	11141	12511	13211	13361	13391	14481	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Axillary, lymphoma malignant histiocytic																								X		1
Inguinal, lymphoma malignant histiocytic																								X		1
Inguinal, sarcoma, metastatic, skin																										1
Lumbar, lymphoma malig histiocytic																								X		1
Mediastinal, lymphoma malig mixed				X																						1
Mesenteric, lymphoma malignant histiocytic																								X		1
Mesenteric, lymphoma malignant lymphocytic																	X									1
Mesenteric, lymphoma malignant mixed				X																						2
Renal, lymphoma malignant histiocytic																								X		1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant histiocytic																								X		1
Lymphoma malignant mixed				X																						2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma			X																							1
Lymphoma malignant lymphocytic								X																		1
Lymphoma malignant mixed				X																						1
Thymus	+	M	M	+	+	+	+	M	M	+	M	M	+	M	+	+	M	M	+	M	+	M	+	M	+	18
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																							X			1
Subcutaneous tissue, fibroma				X												X										3
Subcutaneous tissue, fibrosarcoma		X									X								X							3
Subcutaneous tissue, hepatocholangiocarcinoma, metastatic, liver																										1
Subcutaneous tissue, sarcoma						X								X												4
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma									X				X			X					X		X			5
Alveolar/bronchiolar adenoma, multiple						X																				1
Hepatocellular carcinoma, metastatic, liver																						X				1
Lymphoma malignant mixed				X																						1
Sarcoma, metastatic, skin																										2
Mediastinum, hepatocholangio carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Ear			+																							1
Eye												+														1
Harderian gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	43
Adenoma																						X	X			2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymphoma malignant mixed				X																						2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Control	100 ppm	200 ppm
Adrenal Gland/Medulla: Pheochromocytoma			
Overall Rates (a)	0/31 (0%)	10/45 (22%)	23/45 (51%)
Adjusted Rates (b)	0.0%	37.9%	84.9%
Terminal Rates (c)	0/12 (0%)	7/23 (30%)	18/22 (82%)
Day of First Observation		682	549
Life Table Tests (d)	P<0.001	P=0.021	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.017	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.003	P<0.001
Liver: Hepatocellular Adenoma			
Overall Rates (a)	5/32 (16%)	20/47 (43%)	33/48 (69%)
Adjusted Rates (b)	27.6%	65.2%	88.6%
Terminal Rates (c)	2/12 (17%)	14/24 (58%)	18/22 (82%)
Day of First Observation	330	413	376
Life Table Tests (d)	P<0.001	P=0.074	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.037	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.010	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	2/32 (6%)	10/47 (21%)	12/48 (25%)
Adjusted Rates (b)	11.4%	33.2%	39.7%
Terminal Rates (c)	0/12 (0%)	5/24 (21%)	6/22 (27%)
Day of First Observation	498	521	512
Life Table Tests (d)	P=0.068	P=0.189	P=0.087
Logistic Regression Tests (d)	P=0.046	P=0.127	P=0.049
Cochran-Armitage Trend Test (d)	P=0.031		
Fisher Exact Test (d)		P=0.062	P=0.027
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	7/32 (22%)	26/47 (55%)	37/48 (77%)
Adjusted Rates (b)	35.8%	75.7%	89.7%
Terminal Rates (c)	2/12 (17%)	16/24 (67%)	18/22 (82%)
Day of First Observation	330	413	376
Life Table Tests (d)	P<0.001	P=0.067	P=0.002
Logistic Regression Tests (d)	P<0.001	P=0.015	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.003	P<0.001
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/33 (6%)	(e,f) 1/18 (6%)	6/49 (12%)
Adjusted Rates (b)	16.7%		27.3%
Terminal Rates (c)	2/12 (17%)		6/22 (27%)
Day of First Observation	729		729
Life Table Test (d)			P=0.394
Logistic Regression Test (d)			P=0.394
Fisher Exact Test (d)			P=0.299
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	0/35 (0%)	2/49 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	7.6%	12.3%
Terminal Rates (c)	0/12 (0%)	1/24 (4%)	2/22 (9%)
Day of First Observation		693	654
Life Table Tests (d)	P=0.161	P=0.420	P=0.249
Logistic Regression Tests (d)	P=0.160	P=0.411	P=0.250
Cochran-Armitage Trend Test (d)	P=0.127		
Fisher Exact Test (d)		P=0.337	P=0.193

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Control	100 ppm	200 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	2/35 (6%)	10/49 (20%)	3/49 (6%)
Adjusted Rates (b)	14 4%	31.9%	12 9%
Terminal Rates (c)	1/12 (8%)	5/24 (21%)	2/22 (9%)
Day of First Observation	675	521	701
Life Table Tests (d)	P=0.335N	P=0.187	P=0.597N
Logistic Regression Tests (d)	P=0.347N	P=0.128	P=0.587N
Cochran-Armitage Trend Test (d)	P=0.489N		
Fisher Exact Test (d)		P=0.053	P=0.657
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	2/35 (6%)	12/49 (24%)	6/49 (12%)
Adjusted Rates (b)	14 4%	37.8%	24.4%
Terminal Rates (c)	1/12 (8%)	6/24 (25%)	4/22 (18%)
Day of First Observation	675	521	654
Life Table Tests (d)	P=0 504	P=0.114	P=0.405
Logistic Regression Tests (d)	P=0 497	P=0.069	P=0.418
Cochran-Armitage Trend Test (d)	P=0 334		
Fisher Exact Test (d)		P=0.020	P=0.270
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	2/35 (6%)	0/49 (0%)	4/49 (8%)
Adjusted Rates (b)	11 5%	0.0%	13.5%
Terminal Rates (c)	0/12 (0%)	0/24 (0%)	2/22 (9%)
Day of First Observation	552		446
Life Table Tests (d)	P=0 417	P=0.094N	P=0.652
Logistic Regression Tests (d)	P=0 315	P=0.167N	P=0.522
Cochran-Armitage Trend Test (d)	P=0 323		
Fisher Exact Test (d)		P=0.171N	P=0.509
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	4/35 (11%)	12/49 (24%)	10/49 (20%)
Adjusted Rates (b)	24 2%	37.8%	36.1%
Terminal Rates (c)	1/12 (8%)	6/24 (25%)	6/22 (27%)
Day of First Observation	552	521	446
Life Table Tests (d)	P=0 406	P=0.358	P=0 415
Logistic Regression Tests (d)	P=0 349	P=0 239	P=0 350
Cochran-Armitage Trend Test (d)	P=0 222		
Fisher Exact Test (d)		P=0.110	P=0 216
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/35 (3%)	(g) 2/49 (4%)	3/49 (6%)
Adjusted Rates (b)	3 8%	8 3%	11 4%
Terminal Rates (c)	0/12 (0%)	2/24 (8%)	1/22 (5%)
Day of First Observation	426	729	584
Life Table Tests (d)	P=0 403	P=0 712	P=0 539
Logistic Regression Tests (d)	P=0 365	P=0.661	P=0 460
Cochran-Armitage Trend Test (d)	P=0 323		
Fisher Exact Test (d)		P=0 625	P=0 444
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	1/35 (3%)	(g) 2/49 (4%)	6/49 (12%)
Adjusted Rates (b)	8 3%	6 6%	24 1%
Terminal Rates (c)	1/12 (8%)	1/24 (4%)	4/22 (18%)
Day of First Observation	729	545	640
Life Table Tests (d)	P=0 093	P=0.726N	P=0 221
Logistic Regression Tests (d)	P=0 085	P=0.706	P=0.217
Cochran-Armitage Trend Test (d)	P=0 060		
Fisher Exact Test (d)		P=0 625	P=0.127

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) One carcinoma was also observed.
(g) Twenty-three spleens were examined microscopically.

TABLE A4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	7/50	14/50	19/50
N-Phenyl-2-naphthylamine	6/47	6/47	11/47
C.I. Disperse Yellow 3	7/50	14/50	20/50
D & C Red No. 9	4/50	4/50	8/50
C.I. Solvent Yellow 14	5/49	10/49	15/49
Rotenone	7/47	6/47	12/47
L-Ascorbic acid	6/50	10/50	16/50
TOTAL	42/343 (12.2%)	64/343 (18.7%)	101/343 (29.4%)
SD (b)	2.44%	7.77%	8.42%
Range (c)			
High	7/47	14/50	20/50
Low	4/50	4/50	8/50
Overall Historical Incidence			
TOTAL	259/2,032 (12.7%)	379/2,032 (18.7%)	609/2,032 (30.0%)
SD (b)	7.21%	6.50%	7.59%
Range (c)			
High	22/50	15/50	29/50
Low	0/49	4/50	8/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence of Pheochromocytomas in Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	1/46
N-Phenyl-2-naphthylamine	0/48
C.I. Disperse Yellow 3	1/50
D & C Red No. 9	0/49
C.I. Solvent Yellow 14	0/48
Rotenone	0/47
L-Ascorbic acid	0/50
TOTAL	2/338 (0.6%)
SD (b)	1.02%
Range (c)	
High	1/46
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 30/1,969 (1.5%)
SD (b)	2.11%
Range (c)	
High	4/49
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two malignant pheochromocytomas

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	35	50	50
Animals removed	35	50	50
Animals examined histopathologically	35	49	49
ALIMENTARY SYSTEM			
Intestine large, colon	(27)	(15)	(41)
Parasite metazoan	1 (4%)	1 (7%)	1 (2%)
Intestine small, duodenum	(24)	(12)	(38)
Ulcer	1 (4%)		
Liver	(32)	(47)	(48)
Angiectasis		1 (2%)	2 (4%)
Basophilic focus	2 (6%)	1 (2%)	4 (8%)
Clear cell focus		4 (9%)	6 (13%)
Clear cell focus, multiple		7 (15%)	
Fibrosis	1 (3%)		
Hematopoietic cell proliferation, multifocal	2 (6%)	20 (43%)	27 (56%)
Hyperplasia		6 (13%)	5 (10%)
Infarct	1 (3%)	2 (4%)	1 (2%)
Inflammation, chronic active, diffuse		42 (89%)	46 (96%)
Pigmentation, multifocal		45 (96%)	46 (96%)
Vacuolization cytoplasmic		2 (4%)	
Bile duct, cyst, multiple			1 (2%)
Bile duct, dilatation, focal			1 (2%)
Bile duct, hyperplasia, multifocal		22 (47%)	37 (77%)
Hepatocyte, cytomegaly, diffuse		47 (100%)	48 (100%)
Hepatocyte, necrosis, acute, diffuse		41 (87%)	45 (94%)
Mesentery	(2)		(2)
Inflammation, chronic	1 (50%)		1 (50%)
Salivary glands	(32)	(15)	(48)
Inflammation, acute	1 (3%)		
Inflammation, chronic active			1 (2%)
Stomach, forestomach	(31)	(14)	(43)
Acanthosis			2 (5%)
Cyst	1 (3%)		
Inflammation, chronic active			2 (5%)
Ulcer, chronic active			1 (2%)
Stomach, glandular	(31)	(14)	(42)
Hyperplasia	1 (3%)		
Necrosis	1 (3%)		
Ulcer, acute			1 (2%)
Tooth	(1)		(3)
Peridontal tissue, inflammation, chronic			3 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(33)	(18)	(49)
Degeneration, chronic	2 (6%)	1 (6%)	2 (4%)
Mineralization		1 (6%)	1 (2%)
Atrium, thrombus		2 (11%)	3 (6%)
ENDOCRINE SYSTEM			
Adrenal gland	(31)	(47)	(46)
Capsule, hyperplasia	27 (87%)	33 (70%)	27 (59%)
Adrenal gland, cortex	(31)	(46)	(46)
Degeneration, fatty		2 (4%)	
Hyperplasia			4 (9%)
Hypertrophy	5 (16%)	10 (22%)	6 (13%)
Adrenal gland, medulla	(31)	(45)	(45)
Hyperplasia	1 (3%)	10 (22%)	10 (22%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(29)	(12)	(41)
Pars distalis, cyst	1 (3%)	1 (8%)	
Thyroid gland	(31)	(15)	(47)
Follicle, cyst			1 (2%)
Follicular cell, hyperplasia	3 (10%)		
Follicular cell, hypertrophy	1 (3%)		
GENERAL BODY SYSTEM			
Tissue, NOS			(1)
Inflammation, granulomatous, focal			1 (100%)
GENITAL SYSTEM			
Epididymis	(34)	(17)	(47)
Granuloma sperm		1 (6%)	
Inflammation, acute	1 (3%)		
Inflammation, chronic active			1 (2%)
Penis	(2)	(5)	
Inflammation, acute		1 (20%)	
Inflammation, chronic active		1 (20%)	
Preputial gland	(6)	(6)	(8)
Inflammation, acute			6 (75%)
Inflammation, chronic active	3 (50%)	4 (67%)	
Duct, dilatation	2 (33%)		1 (13%)
Prostate	(34)	(15)	(45)
Inflammation, acute	6 (18%)	1 (7%)	1 (2%)
Inflammation, chronic active	3 (9%)	4 (27%)	3 (7%)
Seminal vesicle	(7)	(4)	(7)
Dilatation	5 (71%)	3 (75%)	6 (86%)
Inflammation, acute			1 (14%)
Inflammation, chronic active	2 (29%)	1 (25%)	1 (14%)
Testes	(34)	(17)	(47)
Inflammation, acute	1 (3%)		
Necrosis			1 (2%)
Germinal epithelium, degeneration	1 (3%)	3 (18%)	3 (6%)
Germinal epithelium, mineralization			2 (4%)
HEMATOPOIETIC SYSTEM			
Blood	(2)	(1)	
Neutrophilia	1 (50%)	1 (100%)	
Bone marrow	(30)	(15)	(44)
Femoral, hyperplasia, neutrophil	2 (7%)	2 (13%)	3 (7%)
Lymph node	(27)	(24)	(44)
Inguinal, infiltration cellular, plasma cell			1 (2%)
Lumbar, hyperplasia, plasma cell		1 (4%)	
Mesenteric, hematopoietic cell proliferation	5 (19%)	10 (42%)	10 (23%)
Mesenteric, hyperplasia, lymphoid			1 (2%)
Renal, hyperplasia, plasma cell	1 (4%)		
Lymph node, mandibular	(27)	(12)	(43)
Depletion lymphoid	1 (4%)		2 (5%)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia, lymphoid			4 (9%)
Hyperplasia, plasma cell	1 (4%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(30)	(23)	(46)
Depletion lymphoid	8 (27%)	3 (13%)	10 (22%)
Lymphoid follicle, necrosis	2 (7%)		
Red pulp, hematopoietic cell proliferation, diffuse	5 (17%)	15 (65%)	18 (39%)
Thymus	(16)	(7)	(18)
Necrosis	1 (6%)		
INTEGUMENTARY SYSTEM			
Skin	(33)	(27)	(49)
Acanthosis	1 (3%)	1 (4%)	
Alopecia		2 (7%)	
Cyst epithelial inclusion			1 (2%)
Foreign body, focal			1 (2%)
Hyperkeratosis		1 (4%)	
Ulcer	3 (9%)	5 (19%)	6 (12%)
Subcutaneous tissue, fibrosis		4 (15%)	
Subcutaneous tissue, inflammation, acute	1 (3%)		
Subcutaneous tissue, inflammation, chronic active	5 (15%)		6 (12%)
Subcutaneous tissue, metaplasia, osseous	1 (3%)		
Subcutaneous tissue, lymphatic, dilatation	1 (3%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(35)	(28)	(48)
Joint, femur, tibia, hyperostosis		1 (4%)	3 (6%)
Joint, tarsal, hyperostosis	11 (31%)	13 (46%)	9 (19%)
Skeletal muscle		(1)	
Mineralization, multifocal		1 (100%)	
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(33)	(18)	(49)
Hemorrhage, acute			1 (2%)
Alveolar epithelium, hyperplasia			2 (4%)
Alveolus, foreign body			4 (8%)
Interstitium, inflammation, acute		1 (6%)	
Interstitium, inflammation, chronic active, multifocal			1 (2%)
Interstitium, mineralization		1 (6%)	
Perivascular, edema, acute			4 (8%)
Perivascular, edema, chronic active			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(2)		(1)
Atrophy, diffuse	1 (50%)		1 (100%)
Lens, cataract	1 (50%)		
Retina, atrophy	1 (50%)		
Harderian gland	(29)	(12)	(43)
Hyperplasia, cystic	1 (3%)		
Acinus, dilatation			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney	(33)	(18)	(47)
Infiltration cellular, plasma cell			1 (2%)
Inflammation, acute	2 (6%)	1 (6%)	4 (9%)
Inflammation, chronic active	1 (3%)	2 (11%)	1 (2%)
Metaplasia, osseous	1 (3%)		
Nephropathy, chronic	11 (33%)	3 (17%)	22 (47%)
Cortex, cyst			1 (2%)
Pelvis, inflammation, acute	1 (3%)	3 (17%)	
Pelvis, inflammation, chronic active	1 (3%)		
Renal tubule, dilatation	2 (6%)		
Renal tubule, mineralization		1 (6%)	1 (2%)
Renal tubule, necrosis	1 (3%)		
Urethra	(6)	(2)	
Calculus micro observation only	2 (33%)	1 (50%)	
Concretion	2 (33%)		
Inflammation, acute	2 (33%)	1 (50%)	
Inflammation, chronic active	1 (17%)		
Urinary bladder	(34)	(15)	(43)
Calculus gross observation			1 (2%)
Calculus micro observation only	1 (3%)		
Concretion	1 (3%)		
Dilatation	6 (18%)	3 (20%)	2 (5%)
Inflammation, acute	5 (15%)	1 (7%)	
Inflammation, chronic active	1 (3%)	2 (13%)	2 (5%)
Necrosis	1 (3%)		
Mucosa, hyperplasia		1 (7%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	35	50	50
Animals removed	35	50	50
Animals examined histopathologically	35	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(30)	*(50)	(45)
Peyer's patch, lymphoma malignant mixed			1 (2%)
Intestine small, ileum	(31)	*(50)	(45)
Peyer's patch, lymphoma malignant lymphocytic		1 (2%)	
Intestine small, jejunum	(32)	*(50)	(46)
Peyer's patch, lymphoma malignant lymphocytic		1 (2%)	
Peyer's patch, lymphoma malignant mixed		1 (2%)	
Liver	(33)	(49)	(50)
Fibrosarcoma, metastatic		1 (2%)	
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, multiple		2 (4%)	3 (6%)
Hepatocellular carcinoma		1 (2%)	1 (2%)
Hepatocellular adenoma	3 (9%)	7 (14%)	7 (14%)
Hepatocellular adenoma, multiple		1 (2%)	1 (2%)
Ito cell tumor benign, multiple		1 (2%)	
Lymphoma malignant histiocytic		1 (2%)	3 (6%)
Lymphoma malignant lymphocytic	1 (3%)	1 (2%)	5 (10%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Mesentery	*(35)	*(50)	*(50)
Fibrosarcoma, metastatic		1 (2%)	
Lymphoma malignant lymphocytic	1 (3%)		
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Pancreas	(31)	*(50)	(48)
Lymphoma malignant lymphocytic	1 (3%)		2 (4%)
Lymphoma malignant mixed			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Salivary glands	(33)	*(50)	(47)
Lymphoma malignant lymphocytic	2 (6%)		5 (11%)
Lymphoma malignant mixed			2 (4%)
Stomach, forestomach	(32)	*(50)	(46)
Papilloma squamous	4 (13%)		
Papilloma squamous, multiple	1 (3%)		
Stomach, glandular	(32)	*(50)	(47)
Lymphoma malignant mixed			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
CARDIOVASCULAR SYSTEM			
Heart	(35)	*(50)	(50)
Lymphoma malignant lymphocytic			2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland	(34)	(48)	(49)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Adrenal gland, cortex	(33)	(48)	(49)
Adenoma	1 (3%)		
Adrenal gland, medulla	(33)	(48)	(49)
Pheochromocytoma malignant	2 (6%)		
Pheochromocytoma benign		1 (2%)	1 (2%)
Bilateral, pheochromocytoma benign		1 (2%)	
Pituitary gland	(32)	*(50)	(39)
Pars distalis, adenoma	11 (34%)	8 (16%)	5 (13%)
Pars distalis, carcinoma			1 (3%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(33)	*(50)	(48)
Lymphoma malignant lymphocytic			1 (2%)
C-cell, adenoma			1 (2%)
Follicular cell, adenoma			1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(35)	*(50)	*(50)
Lymphoma malignant histiocytic			1 (2%)
GENITAL SYSTEM			
Ovary	(30)	*(50)	(48)
Adenoma	2 (7%)	1 (2%)	
Carcinoma		1 (2%)	
Granulosa cell tumor malignant			1 (2%)
Hemangiosarcoma			1 (2%)
Luteoma	1 (3%)	2 (4%)	1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	2 (7%)		5 (10%)
Lymphoma malignant mixed			3 (6%)
Uterus	(33)	*(50)	(48)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant mixed			1 (2%)
Polyp stromal		1 (2%)	1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(35)	*(50)	(49)
Femoral, hemangiosarcoma			2 (4%)
Femoral, lymphoma malignant histiocytic			2 (4%)
Femoral, lymphoma malignant lymphocytic	1 (3%)		
Lymph node	(33)	*(50)	(46)
Bronchial, lymphoma malignant histiocytic			1 (2%)
Bronchial, lymphoma malignant lymphocytic	1 (3%)		
Inguinal, lymphoma malignant lymphocytic	1 (3%)		
Inguinal, lymphoma malignant mixed			1 (2%)
Lumbar, lymphoma malignant lymphocytic	2 (6%)		1 (2%)
Lumbar, lymphoma malignant mixed			1 (2%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Mediastinal, lymphoma malignant histiocytic	1 (3%)		2 (4%)
Mediastinal, lymphoma malignant lymphocytic	4 (12%)		3 (7%)
Mediastinal, lymphoma malignant mixed	1 (3%)		3 (7%)
Mediastinal, sarcoma, metastatic, uncertain primary site	1 (3%)		
Mesenteric, lymphoma malignant histiocytic	1 (3%)	1 (2%)	2 (4%)
Mesenteric, lymphoma malignant lymphocytic	7 (21%)	3 (6%)	4 (9%)
Mesenteric, lymphoma malignant mixed		1 (2%)	2 (4%)
Pancreatic, lymphoma malignant lymphocytic	1 (3%)		
Renal, lymphoma malignant histiocytic	1 (3%)		
Renal, lymphoma malignant lymphocytic	2 (6%)		1 (2%)
Renal, lymphoma malignant mixed	1 (3%)		
Lymph node, mandibular	(33)	*(50)	(45)
Hemangiosarcoma			1 (2%)
Lymphoma malignant histiocytic	1 (3%)		1 (2%)
Lymphoma malignant lymphocytic	11 (33%)		8 (18%)
Lymphoma malignant mixed			4 (9%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(33)	*(50)	(47)
Fibrosarcoma		1 (2%)	
Hemangiosarcoma		1 (2%)	3 (6%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic	12 (36%)	4 (8%)	6 (13%)
Lymphoma malignant mixed		1 (2%)	4 (9%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Thymus	(28)	*(50)	(33)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)
Lymphoma malignant histiocytic	1 (4%)	1 (2%)	1 (3%)
Lymphoma malignant lymphocytic	3 (11%)		1 (3%)
Lymphoma malignant mixed			1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(30)	*(50)	(34)
Adenoacanthoma			1 (3%)
Adenocarcinoma	3 (10%)	2 (4%)	1 (3%)
Carcinoma			1 (3%)
Skin	(33)	*(50)	(48)
Squamous cell carcinoma			1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)	2 (4%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, lymphoma malignant histiocytic			2 (4%)
Subcutaneous tissue, lymphoma malignant lymphocytic			1 (2%)
Subcutaneous tissue, lymphoma malignant mixed			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(35)	*(50)	(49)
Lumbar, vertebra, osteosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(33)	*(50)	(49)
Lymphoma malignant lymphocytic			2 (4%)
Spinal cord	*(35)	*(50)	*(50)
Osteosarcoma, metastatic, bone			1 (2%)
RESPIRATORY SYSTEM			
Lung	(35)	*(50)	(50)
Adenoacanthoma, metastatic, mammary gland			1 (2%)
Alveolar/bronchiolar adenoma		1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (3%)		1 (2%)
Fibrosarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic	1 (3%)		4 (8%)
Lymphoma malignant mixed			1 (2%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Mediastinum, lymphoma malignant lymphocytic			1 (2%)
Mediastinum, lymphoma malignant mixed			1 (2%)
Nose	(35)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Harderian gland	*(35)	*(50)	*(50)
Adenoma	2 (6%)		1 (2%)
URINARY SYSTEM			
Kidney	(33)	*(50)	(49)
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic	6 (18%)	1 (2%)	7 (14%)
Lymphoma malignant mixed	1 (3%)	1 (2%)	3 (6%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
Urinary bladder	(32)	*(50)	(47)
Lymphoma malignant lymphocytic			4 (9%)
Lymphoma malignant mixed			2 (4%)
Sarcoma, metastatic, uncertain primary site	1 (3%)		
SYSTEMIC LESIONS			
Multiple organs	*(35)	*(50)	*(50)
Lymphoma malignant lymphocytic	12 (34%)	6 (12%)	9 (18%)
Lymphoma malignant histiocytic	1 (3%)	1 (2%)	4 (8%)
Lymphoma malignant mixed	1 (3%)	2 (4%)	5 (10%)
Hemangiosarcoma		3 (6%)	6 (12%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	35	50	50
Terminal sacrifice	28	41	30
Natural death	7	8	15
Moribund sacrifice		1	5
TUMOR SUMMARY			
Total animals with primary neoplasms **	27	30	37
Total primary neoplasms	45	42	56
Total animals with benign neoplasms	17	17	19
Total benign neoplasms	25	24	21
Total animals with malignant neoplasms	18	17	30
Total malignant neoplasms	20	18	35
Total animals with secondary neoplasms ***	1	1	4
Total secondary neoplasms	11	2	6
Total animals with malignant neoplasms uncertain primary site	1		

* Number of animals receiving complete necropsy examination, all gross lesions including masses examined microscopically
** Primary tumors all tumors except secondary tumors
*** Secondary tumors metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	022	027	087	091	091	097	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	373	423	414	383	422	402	362	365	372	382	391	401	403	411	413	415	361	363	364	371	375	393	395	404	421
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	M	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	M	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	M	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					
Lymphoma malignant lymphocytic																								X	
Sarcoma, metastatic, uncertain primary site							X																		
Mesentery							+							+											
Lymphoma malignant lymphocytic														X											
Sarcoma, metastatic, uncertain primary site							X																		
Pancreas	+	+	I	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Sarcoma, metastatic, uncertain primary site							X																		
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									
Stomach	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Papilloma squamous										X		X													
Papilloma squamous, multiple																									
Stomach, glandular	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site							X																		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site							X																		
Adrenal gland, cortex	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant			X									X													
Islets, pancreatic	+	+	I	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X						X	X		X		X		X			
Thyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	A	M	+	M	+	+	+	+	+	+	+	A	+	+	+	+	I	+	+	+	+	+
Adenoma										X															
Luteoma																									
Lymphoma malignant lymphocytic																						X			
Uterus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site							X																		

\+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A. Autolysis precludes examination
X Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	42 4	37 4	38 1	38 4	38 5	39 2	39 4	40 5	41 2	42 5	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	33
Gallbladder	+	+	+	+	+	+	+	+	+	+	29
Intestine large	+	+	+	+	+	+	+	+	+	+	32
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	30
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	32
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	31
Intestine small	+	+	+	+	+	+	+	+	+	+	32
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	32
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	31
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	+	+	+	33
Hepatocellular adenoma			X							X	3
Lymphoma malignant lymphocytic											1
Sarcoma, metastatic, uncertain primary site											1
Mesentery						+					3
Lymphoma malignant lymphocytic											1
Sarcoma, metastatic, uncertain primary site											1
Pancreas	+	+	+	+	+	+	+	+	+	+	31
Lymphoma malignant lymphocytic			X								1
Sarcoma, metastatic, uncertain primary site											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant lymphocytic									X		2
Stomach	+	+	+	+	+	+	+	+	+	+	32
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	32
Papilloma squamous			X							X	4
Papilloma squamous, multiple								X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	32
Sarcoma, metastatic, uncertain primary site											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	35
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	34
Sarcoma, metastatic, uncertain primary site											1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	33
Adenoma				X							1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	33
Pheochromocytoma malignant											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	31
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	32
Pars distalis, adenoma			X	X		X				X	11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	33
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Ovary	+	+	+	+	+	+	+	+	+	+	30
Adenoma										X	2
Luteoma	X										1
Lymphoma malignant lymphocytic			X								2
Uterus	+	+	+	+	+	+	+	+	+	+	33
Sarcoma, metastatic, uncertain primary site											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	022	027	087	091	091	097	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	373	423	414	383	422	402	362	365	372	382	391	401	403	411	413	415	361	363	364	371	375	393	395	404	421
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, lymphoma malignant lymphocytic																									
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant lymphocytic																									
Inguinal, lymphoma malignant lymphocytic				X																					
Lumbar, lymphoma malignant lymphocytic																									X
Mediastinal, lymphoma malignant histiocytic					X																				
Mediastinal, lymphoma malignant lymphocytic				X												X									X
Mediastinal, lymphoma malignant mixed																									
Mediastinal, sarcoma, metastatic, uncertain primary site							X																		
Mesenteric, lymphoma malignant histiocytic					X																				
Mesenteric, lymphoma malignant lymphocytic				X										X		X		X							X
Pancreatic, lymphoma malignant lymphocytic																						X			
Renal, lymphoma malignant histiocytic					X																				
Renal, lymphoma malignant lymphocytic				X																					X
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic				X										X		X		X				X		X	X
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic				X										X		X		X			X	X		X	X
Sarcoma, metastatic, uncertain primary site							X																		
Thymus	+	M	+	M	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic																X									X
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	M	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma															X										
Lymphoma malignant lymphocytic																X									
Sarcoma, metastatic, uncertain primary site							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma								X								X									
URINARY SYSTEM																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																X									X
Lymphoma malignant mixed																									
Sarcoma, metastatic, uncertain primary site							X																		
Urinary bladder	+	+	+	A	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site							X																		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	424	374	381	384	385	392	394	405	412	425	TISSUES TUMORS
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	35
Femoral, lymphoma malignant lymphocytic			X								1
Lymph node	+	+	+	+	+	+	+	+	+	+	33
Bronchial, lymphoma malignant lymphocytic				X							1
Inguinal, lymphoma malignant lymphocytic											1
Lumbar, lymphoma malig. lymphocytic		X									2
Mediastinal, lymphoma malignant histiocytic											1
Mediastinal, lymphoma malignant lymphocytic				X							4
Mediastinal, lymphoma malig. mixed	X										1
Mediastinal, sarcoma, metastatic, uncertain primary site											1
Mesenteric, lymphoma malignant histiocytic											1
Mesenteric, lymphoma malignant lymphocytic			X	X							7
Pancreatic, lymphoma malignant lymphocytic											1
Renal, lymphoma malignant histiocytic											1
Renal, lymphoma malig. lymphocytic											2
Renal, lymphoma malignant mixed	X										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic		X	X	X					X		11
Spleen	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant lymphocytic		X	X	X					X		12
Sarcoma, metastatic, uncertain primary site											1
Thymus	M	+	+	+	+	+	+	+	+	+	28
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic		X									3
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	30
Adenocarcinoma		X			X						3
Skin	+	+	+	+	+	+	+	+	+	+	33
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	35
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	33
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	35
Alveolar/bronchiolar carcinoma											1
Lymphoma malignant lymphocytic											1
Sarcoma, metastatic, uncertain primary site											1
Nose	+	+	+	+	+	+	+	+	+	+	35
Trachea	+	+	+	+	+	+	+	+	+	+	33
SPECIAL SENSES SYSTEM											
Harderian gland	+	+	+	+	+	+	+	+	+	+	32
Adenoma											2
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant lymphocytic		X	X	X					X		6
Lymphoma malignant mixed	X										1
Sarcoma, metastatic, uncertain primary site											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	32
Sarcoma, metastatic, uncertain primary site											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	055	061	065	068	094	097	099	101	101	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	0995	0982	1022	1025	0964	0944	0992	1011	1015	0931	0941	0952	0953	0955	0961	0973	0981	0985	0994	1002	1004	1013	0932	0934	0942
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+																					
Gallbladder	A	A	M	A																					
Intestine large	+	A	+	+																					
Intestine large, cecum	+	A	+	A																					
Intestine large, colon	+	A	+	+																					
Intestine large, rectum	+	A	M	+																					
Intestine small	+	A	+	+																					+
Intestine small, duodenum	+	A	+	+																					
Intestine small, ileum	A	A	M	A																					+
Peyer's patch, lymphoma malignant lymphocytic																									X
Intestine small, jejunum	+	A	+	+																					+
Peyer's patch, lymphoma malignant lymphocytic																									X
Peyer's patch, lymphoma malignant mixed																									
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic								X																	
Hemangiosarcoma, multiple		X								X															
Hepatocellular carcinoma									X																
Hepatocellular adenoma														X									X		
Hepatocellular adenoma, multiple											X														
Ito cell tumor benign, multiple										X															
Lymphoma malignant histiocytic							X																		
Lymphoma malignant lymphocytic																		X							
Mesentery								+																	
Fibrosarcoma, metastatic								X																	
Pancreas	+	A	+	+	+																				
Salivary glands	+	+	+	+																					
Stomach	+	A	+	+																					
Stomach, forestomach	+	A	+	+																					
Stomach, glandular	+	A	+	+																					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+																					
ENDOCRINE SYSTEM																									
Adrenal gland	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X											
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	A	+	+																					
Parathyroid gland	+	+	+	+																					
Pituitary gland	M	M	+	+	+						+	+							+					+	+
Pars distalis, adenoma											X	X												X	X
Thyroid gland	+	+	+	+																					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+		+				+	+		+		+			+	+		+	+			+
Adenoma																									
Carcinoma	X																								
Luteoma																			X						
Uterus	+	+	+	+	+									+	+	+	+	+		+	+	+	+	+	+
Polyp stromal																								X	

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	09455	09551	09662	09665	09772	09774	09883	09884	10105	10223	10224	09933	09935	09943	09955	09963	09971	09975	09991	09993	10001	10003	10112	10114	10211	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										4
Gallbladder																										
Intestine large																										3
Intestine large, cecum																										2
Intestine large, colon																										3
Intestine large, rectum																										2
Intestine small									+																	5
Intestine small, duodenum																										3
Intestine small, ileum																										1
Peyer's patch, lymphoma malignant lymphocytic																										1
Intestine small, jejunum									+																	5
Peyer's patch, lymphoma malignant lymphocytic																										1
Peyer's patch, lymphoma malignant mixed									X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
Hemangiosarcoma, multiple																										2
Hepatocellular carcinoma																										1
Hepatocellular adenoma		X				X												X			X	X				7
Hepatocellular adenoma, multiple																										1
Ito cell tumor benign, multiple																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Mesentery																										1
Fibrosarcoma, metastatic																										1
Pancreas																										4
Salivary glands																										4
Stomach																										3
Stomach, forestomach																										3
Stomach, glandular																										3
CARDIOVASCULAR SYSTEM																										
Heart																										4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic																										3
Parathyroid gland																										4
Pituitary gland		+			+		+						+					+				+				14
Pars distalis, adenoma		X			X													X				X				8
Thyroid gland																										4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	I					+					+	+	+	+		+		+					+		23
Adenoma																	X									1
Carcinoma																										1
Luteoma													X													2
Uterus	+		+	+		+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Polyp stromal																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	055	061	065	068	094	097	099	101	101	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	09955	09982	10225	10255	09964	09944	09932	10111	10115	09931	09941	09952	09953	09954	09961	09973	09981	09985	09994	10024	10043	10132	09932	09934	09942
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+																					
Lymph node	+	+	+	+			+			+							+								
Mesenteric, lymphoma malignant histiocytic							X																		
Mesenteric, lymphoma malignant lymphocytic																	X								
Mesenteric, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+																					
Spleen	+	+	+	+	+	+				+	+						+	+				+			
Fibrosarcoma										X															
Hemangiosarcoma											X														
Lymphoma malignant lymphocytic																	X	X				X			
Lymphoma malignant mixed																									
Thymus	M	M	+	M			+																		
Lymphoma malignant histiocytic							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	M	+								+												
Adenocarcinoma					X								X												
Skin	+	+	+	+				+																	
Subcutaneous tissue, fibrosarcoma								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+																					
NERVOUS SYSTEM																									
Brain	+	+	+	+			A																		
RESPIRATORY SYSTEM																									
Lung	+	+	+	+											+										
Alveolar/bronchiolar adenoma															X										
Nose	+	+	+	+																					
Trachea	+	+	+	+																					
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+																					
URINARY SYSTEM																									
Kidney	+	+	+	+			+										+								
Lymphoma malignant lymphocytic																	X								
Lymphoma malignant mixed																									
Urinary bladder	+	A	+	+																					

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	09455	09551	09662	09665	09772	09774	09883	09884	10005	10223	10224	10933	10935	10943	10955	10963	10971	10975	10991	10993	11001	11003	11012	11014	11021	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										4
Lymph node									+	+			+	+								+				12
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant lymphocytic										X				X												3
Mesenteric, lymphoma malignant mixed									X																	1
Lymph node, mandibular																										4
Spleen									+	+																13
Fibrosarcoma																										1
Hemangiosarcoma																										1
Lymphoma malignant lymphocytic										X																4
Lymphoma malignant mixed									X																	1
Thymus																										2
Lymphoma malignant histiocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland																										3
Adenocarcinoma																										2
Skin																										5
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										4
NERVOUS SYSTEM																										
Brain																										4
RESPIRATORY SYSTEM																										
Lung																										5
Alveolar/bronchiolar adenoma																										1
Nose																										4
Trachea																										4
SPECIAL SENSES SYSTEM																										
Harderian gland																										4
URINARY SYSTEM																										
Kidney																						+				7
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																						X				1
Urinary bladder																										3

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	0 3 2	0 5 1	0 5 9	0 6 2	0 7 1	0 7 9	0 8 9	0 9 1	0 9 4	0 9 5	0 9 7	0 9 7	0 9 8	0 9 8	1 0 0	1 0 0	1 0 2	1 0 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	1 5 9 3	1 6 1 3	1 6 1 2	1 5 9 1	1 5 5 2	1 6 2 1	1 5 4 1	1 5 3 1	1 6 2 2	1 5 9 5	1 5 3 5	1 5 9 2	1 6 1 4	1 5 5 3	1 5 6 1	1 5 7 4	1 5 3 4	1 5 6 4	1 5 3 3	1 5 5 5	1 5 6 2	1 5 6 5	1 5 7 1	1 5 8 4	1 5 8 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	+	A	+	A	A	A	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+
Intestine large	M	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant mixed																									
Intestine large, colon	M	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, multiple															X		X	X							
Hepatocellular carcinoma											X														
Hepatocellular adenoma														X									X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic				X				X												X					
Lymphoma malignant lymphocytic	X					X							X												
Pancreas	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Salivary glands	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed																									
Stomach	M	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	M	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic	X																								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	+	+	M	M	M	M	+	+	+	+	+	M	M	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pars distalis, adenoma																X		X							
Pars distalis, carcinoma													X												
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
C cell, adenoma																									
Follicular cell, adenoma													X												
GENERAL BODY SYSTEM																									
Tissue, NOS								+																	
Lymphoma malignant histiocytic								X																	
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Hemangiosarcoma																									
Luteoma																									
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed																									
Uterus	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																									
Polyp stromal																				X					

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	15944	16033	16111	16244	16255	15422	15433	15455	15544	15633	15733	15755	16001	16044	16055	16155	15532	15444	15511	15721	15811	15822	15833	16022	16233	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		47
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	-	+	+	+	+	A	+	+		39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		45
Peyer's patch, lymphoma malignant mixed				X																						1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+		45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+		45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																						X				1
Hemangiosarcoma, multiple																										3
Hepatocellular carcinoma																										1
Hepatocellular adenoma		X				X					X				X							X				7
Hepatocellular adenoma, multiple																									X	1
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic													X											X		5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant lymphocytic		X							X																	2
Lymphoma malignant mixed					X																					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		47
Lymphoma malignant lymphocytic		X	X						X				X													5
Lymphoma malignant mixed					X											X										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Lymphoma malignant mixed					X																					1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic		X																								2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+		35
Pituitary gland	M	+	+	+	+	+	+	+	I	+	M	M	+	+	+	+	+	M	+	+	M	M	+	+		39
Pars distalis, adenoma			X		X														X							5
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
Lymphoma malignant lymphocytic		X																								1
C-cell, adenoma											X															1
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Lymphoma malignant histiocytic																										1
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Granulosa cell tumor malignant							X																			1
Hemangiosarcoma													X													1
Luteoma											X															1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X							X				X											X		5
Lymphoma malignant mixed					X											X						X				3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X																								2
Lymphoma malignant mixed					X																					1
Polyp stromal																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	032	051	059	062	071	079	089	091	094	095	097	097	098	098	100	100	102	102	105	105	105	105	105	105	105
CARCASS ID	15933	16133	16132	15911	15552	16221	15411	15331	16222	15955	15335	15992	16114	15553	15611	15734	15334	15644	15333	15555	15562	15565	15571	15844	15885
HEMATOPOIETIC SYSTEM																									
Blood																									+
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma																	X	X							
Femoral, lymphoma malignant histiocytic				X						X															
Lymph node	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Bronchial, lymphoma malignant histiocytic								X																	
Inguinal, lymphoma malignant mixed																									
Lumbar, lymphoma malignant lymphocytic													X												
Lumbar, lymphoma malignant mixed																									
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung															X										
Mediastinal, lymphoma malignant histiocytic								X		X															
Mediastinal, lymphoma malignant lymphocytic													X												
Mediastinal, lymphoma malignant mixed															X										
Mesenteric, lymphoma malignant histiocytic								X		X															
Mesenteric, lymphoma malignant lymphocytic						X							X												
Mesenteric, lymphoma malignant mixed															X										
Renal, lymphoma malignant lymphocytic													X												
Lymph node, mandibular	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic						X							X												
Lymphoma malignant mixed															X										
Spleen	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X	X							
Lymphoma malignant histiocytic																				X					
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed															X										
Thymus	M	M	+	M	M	+	M	M	+	+	M	+	M	M	+	M	M	+	+	+	M	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	M	+	M	M	+	+	M	M	+	M	+	M	+	+	+	+	M	+
Adenoacanthoma																									
Adenocarcinoma																									
Carcinoma		X																							
Skin	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Subcutaneous tissue, fibrosarcoma									X					X											
Subcutaneous tissue, hemangiosarcoma																	X								
Subcutaneous tissue, lymphoma malignant histiocytic				X						X															
Subcutaneous tissue, lymphoma malignant lymphocytic																									
Subcutaneous tissue, lymphoma malignant mixed																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Lumbar, vertebra, osteosarcoma												X													
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Spinal cord												+													
Osteosarcoma, metastatic, bone												X													

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	15944	16003	16111	16244	16255	15442	15433	15455	15544	15634	15733	15755	16001	16044	16055	16155	15332	15444	15551	15721	15881	15882	15883	16022	16233	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood										+																2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, hemangiosarcoma																										2
Femoral, lymphoma malignant histiocytic																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Bronchial, lymphoma malignant histiocytic																										1
Inguinal, lymphoma malignant mixed					X																					1
Lumbar, lymphoma malig. lymphocytic																										1
Lumbar, lymphoma malignant mixed																X										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malignant lymphocytic									X				X													3
Mediastinal, lymphoma malig. mixed					X											X										3
Mesenteric, lymphoma malignant histiocytic																										2
Mesenteric, lymphoma malignant lymphocytic													X						X							4
Mesenteric, lymphoma malignant mixed																X										2
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X	X						X				X						X					X		8
Lymphoma malignant mixed					X											X						X				4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma						X																				3
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X	X						X				X											X		6
Lymphoma malignant mixed				X												X						X				4
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	33
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic		X																								1
Lymphoma malignant mixed																X										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	M	M	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	34
Adenoacanthoma										X																1
Adenocarcinoma																							X			1
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lymphoma malignant histiocytic																										2
Subcutaneous tissue, lymphoma malignant lymphocytic		X																								1
Subcutaneous tissue, lymphoma malignant mixed					X																					1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lumbar, vertebra, osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic													X													2
Spinal cord																										1
Osteosarcoma, metastatic, bone																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	032	051	059	062	071	079	089	091	094	095	097	097	098	098	100	100	102	102	105	105	105	105	105	105	105
CARCASS ID	15993	16113	16112	15911	15552	16211	15411	15311	16225	15955	15335	15922	16144	15533	15561	15744	15334	15664	15333	15555	15662	15665	15715	15844	15885
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma															X										
Fibrosarcoma, metastatic, skin									X																
Lymphoma malignant histiocytic				X						X															
Lymphoma malignant lymphocytic	X																								
Lymphoma malignant mixed																									
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung															X										
Mediastinum, lymphoma malignant lymphocytic	X																								
Mediastinum, lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X																			
Trachea	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X						X															
Lymphoma malignant lymphocytic						X							X												
Lymphoma malignant mixed															X										
Urinary bladder	A	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	15994	16003	16111	16244	16285	15422	15433	15455	15554	15633	15733	15755	16001	16044	16065	16115	15532	15444	15511	15722	15811	15822	15833	16022	16233	
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma, metastatic, mammary gland										X																1
Alveolar/bronchiolar adenoma									X															X		2
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic		X											X											X		4
Lymphoma malignant mixed																X										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinum, lymphoma malignant lymphocytic																										1
Mediastinum, lymphoma malig mixed					X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X									1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic		X	X						X				X											X		7
Lymphoma malignant mixed					X											X										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic		X	X										X													4
Lymphoma malignant mixed					X											X										2

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Control	100 ppm	200 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/33 (9%)	8/49 (16%)	8/50 (16%)
Adjusted Rates (b)	10.7%	19.5%	24.0%
Terminal Rates (c)	3/28 (11%)	8/41 (20%)	7/32 (22%)
Day of First Observation	729	729	682
Life Table Tests (d)	P=0.113	P=0.261	P=0.148
Logistic Regression Tests (d)	P=0.151	P=0.261	P=0.193
Cochran-Armitage Trend Test (d)	P=0.258		
Fisher Exact Test (d)		P=0.275	P=0.287
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/33 (9%)	9/49 (18%)	9/50 (18%)
Adjusted Rates (b)	10.7%	21.4%	25.9%
Terminal Rates (c)	3/28 (11%)	8/41 (20%)	7/32 (22%)
Day of First Observation	729	707	673
Life Table Tests (d)	P=0.080	P=0.193	P=0.104
Logistic Regression Tests (d)	P=0.131	P=0.227	P=0.154
Cochran-Armitage Trend Test (d)	P=0.198		
Fisher Exact Test (d)		P=0.200	P=0.211
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/35 (3%)	(e) 1/5 (20%)	3/50 (6%)
Adjusted Rates (b)	3.4%		8.9%
Terminal Rates (c)	1/29 (3%)		2/32 (6%)
Day of First Observation	729		694
Life Table Test (d)			P=0.353
Logistic Regression Test (d)			P=0.400
Fisher Exact Test (d)			P=0.453
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	3/35 (9%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	10.3%	4.6%	3.1%
Terminal Rates (c)	3/29 (10%)	1/41 (2%)	1/32 (3%)
Day of First Observation	729	656	729
Life Table Tests (d)	P=0.174N	P=0.339N	P=0.269N
Logistic Regression Tests (d)	P=0.136N	P=0.333N	P=0.269N
Cochran-Armitage Trend Test (d)	P=0.125N		
Fisher Exact Test (d)		P=0.334N	P=0.187N
Mammary Gland: Adenocarcinoma or Carcinoma			
Overall Rates (a)	3/35 (9%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	10.3%	4.6%	5.1%
Terminal Rates (c)	3/29 (10%)	1/41 (2%)	1/32 (3%)
Day of First Observation	729	656	356
Life Table Tests (d)	P=0.333N	P=0.339N	P=0.429N
Logistic Regression Tests (d)	P=0.261N	P=0.333N	P=0.337N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.334N	P=0.334N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	11/32 (34%)	(e) 8/14 (57%)	5/39 (13%)
Adjusted Rates (b)	37.7%		17.6%
Terminal Rates (c)	10/28 (36%)		3/24 (13%)
Day of First Observation	605		695
Life Table Test (d)			P=0.115N
Logistic Regression Test (d)			P=0.044N
Fisher Exact Test (d)			P=0.030N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Control	100 ppm	200 ppm
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	11/32 (34%)	(e) 8/14 (57%)	6/39 (15%)
Adjusted Rates (b)	37 7%		19 7%
Terminal Rates (c)	10/28 (36%)		3/24 (13%)
Day of First Observation	605		681
Life Table Test (d)			P=0 178N
Logistic Regression Test (d)			P=0 077N
Fisher Exact Test (d)			P=0 056N
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	5/32 (16%)	(e) 0/3 (0%)	0/46 (0%)
Adjusted Rates (b)	17 9%		0 0%
Terminal Rates (c)	5/28 (18%)		0/31 (0%)
Day of First Observation	729		
Life Table Test (d)			P=0 024N
Logistic Regression Test (d)			P=0 024N
Fisher Exact Test (d)			P=0 010N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	0/35 (0%)	(f) 3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	0 0%	6 8%	17 1%
Terminal Rates (c)	0/29 (0%)	2/41 (5%)	3/32 (9%)
Day of First Observation		424	694
Life Table Tests (d)	P=0 013	P=0 194	P=0 029
Logistic Regression Tests (d)	P=0 024	P=0 152	P=0 036
Cochran Armitage Trend Test (d)	P=0 024		
Fisher Exact Test (d)		P=0 198	P=0 036
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/35 (40%)	(f) 9/50 (18%)	18/50 (36%)
Adjusted Rates (b)	45 0%	21 3%	44 5%
Terminal Rates (c)	12/29 (41%)	8/41 (20%)	11/32 (34%)
Day of First Observation	635	692	224
Life Table Tests (d)	P=0 349	P=0 026N	P=0 457
Logistic Regression Tests (d)	P=0 501N	P=0 019N	P=0 444N
Cochran Armitage Trend Test (d)	P=0 495N		
Fisher Exact Test (d)		P=0 023N	P=0 440N

(a) Number of tumor bearing animals/number of animals examined at the site
(b) Kaplan Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death The logistic regression test regards these lesions as nonfatal The Cochran Armitage and Fisher exact tests compare directly the overall incidence rates A negative trend or lower incidence in a dosed group is indicated by (N)
(e) Incomplete sampling of tissues
(f) Thirteen spleens were examined microscopically

TABLE B4a. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	1/50	0/50	1/50
N-Phenyl-2-naphthylamine	0/50	0/50	0/50
C.I. Disperse Yellow 3	0/50	0/50	0/50
D & C Red No. 9	0/50	2/50	2/50
C.I. Solvent Yellow 14	0/50	1/50	1/50
Rotenone	0/49	0/49	0/49
L-Ascorbic acid	1/50	2/50	3/50
TOTAL	2/349 (0.6%)	5/349 (1.4%)	7/349 (2.0%)
SD (b)	0.98%	1.90%	2.31%
Range (c)			
High	1/50	2/50	3/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	30/2,040 (1.5%)	(d) 33/2,040 (1.6%)	(d) 66/2,040 (3.2%)
SD (b)	2.03%	2.06%	2.73%
Range (c)			
High	4/50	4/50	6/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes nine angiosarcomas

TABLE B4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/48	4/48	8/48
N-Phenyl-2-naphthylamine	3/50	1/50	4/50
C.I. Disperse Yellow 3	0/50	2/50	2/50
D & C Red No. 9	1/50	4/50	5/50
C.I. Solvent Yellow 14	0/50	2/50	2/50
Rotenone	3/49	1/49	4/49
L-Ascorbic acid	2/50	(b) 1/50	3/50
TOTAL	13/347 (3.7%)	15/347 (4.3%)	28/347 (8.1%)
SD (c)	3.24%	2.76%	4.38%
Range (d)			
High	4/48	4/48	8/48
Low	0/50	1/50	2/50
Overall Historical Incidence			
TOTAL	107/2,032 (5.3%)	(b) 81/2,032 (4.0%)	184/2,032 (9.1%)
SD (c)	4.34%	2.42%	4.70%
Range (d)			
High	9/49	4/48	10/49
Low	0/50	0/50	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) One hepatoblastoma was also observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	35	50	50
Animals removed	35	50	50
Animals examined histopathologically	35	50	50
ALIMENTARY SYSTEM			
Intestine large, colon	(32)	(3)	(47)
Parasite metazoan			1 (2%)
Intestine small, duodenum	(32)	(3)	(47)
Mineralization			1 (2%)
Liver	(33)	(49)	(50)
Basophilic focus	1 (3%)		5 (10%)
Clear cell focus	1 (3%)	3 (6%)	7 (14%)
Clear cell focus, multiple			10 (20%)
Degeneration, cystic	1 (3%)	1 (2%)	
Hematopoietic cell proliferation, multifocal	14 (42%)	8 (16%)	33 (66%)
Hyperplasia			3 (6%)
Infarct	4 (12%)	2 (4%)	2 (4%)
Inflammation, chronic active, diffuse		34 (69%)	44 (88%)
Pigmentation, multifocal		37 (76%)	47 (94%)
Vacuolization cytoplasmic	1 (3%)	3 (6%)	
Bile duct, hyperplasia, multifocal		1 (2%)	2 (4%)
Bile duct, inflammation, chronic active, multifocal		1 (2%)	
Hepatocyte, cytomegaly, diffuse		48 (98%)	48 (96%)
Hepatocyte, necrosis, acute, diffuse		44 (90%)	47 (94%)
Mesentery	(3)	(1)	
Inflammation, chronic	1 (33%)		
Pancreas	(31)	(4)	(48)
Acinus, atrophy	4 (13%)		6 (13%)
Acinus, inflammation, chronic			1 (2%)
Duct, cyst			2 (4%)
Salivary glands	(33)	(4)	(47)
Hyperplasia, lymphoid			1 (2%)
Stomach, forestomach	(32)	(3)	(46)
Acanthosis	4 (13%)		3 (7%)
Erosion			1 (2%)
Inflammation, chronic active	3 (9%)		1 (2%)
Ulcer, acute	2 (6%)		
Stomach, glandular	(32)	(3)	(47)
Dysplasia	1 (3%)		
CARDIOVASCULAR SYSTEM			
Heart	(35)	(4)	(50)
Mineralization			1 (2%)
Perivascular, inflammation, chronic active			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(34)	(48)	(49)
Capsule, hyperplasia	33 (97%)	48 (100%)	49 (100%)
Adrenal gland, cortex	(33)	(48)	(49)
Atrophy		1 (2%)	
Degeneration, fatty		1 (2%)	
Hematopoietic cell proliferation		1 (2%)	2 (4%)
Hyperplasia	1 (3%)	2 (4%)	3 (6%)
Hypertrophy	1 (3%)	2 (4%)	4 (8%)
Adrenal gland, medulla	(33)	(48)	(49)
Hyperplasia		4 (8%)	2 (4%)
Parathyroid gland	(30)	(4)	(35)
Infiltration cellular, lymphocytic	1 (3%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(32)	(14)	(39)
Pars distalis, cyst	1 (3%)	1 (7%)	
Pars distalis, hyperplasia	10 (31%)	4 (29%)	10 (26%)
Thyroid gland	(33)	(4)	(48)
Inflammation, chronic	3 (9%)		
Follicular cell, hyperplasia	7 (21%)		1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(30)	(23)	(48)
Angiectasis			1 (2%)
Inflammation, chronic active		1 (4%)	1 (2%)
Mineralization		1 (4%)	
Follicle, cyst	8 (27%)	9 (39%)	15 (31%)
Periovarian tissue, cyst	2 (7%)	10 (43%)	3 (6%)
Uterus	(33)	(37)	(48)
Inflammation, chronic active	1 (3%)		
Endometrium, hyperplasia, cystic, glandular, multifocal	28 (85%)	35 (95%)	35 (73%)
HEMATOPOIETIC SYSTEM			
Blood			(2)
Leukocytosis			1 (50%)
Neutrophilia			1 (50%)
Bone marrow	(35)	(4)	(49)
Femoral, hyperplasia, neutrophil			2 (4%)
Femoral, myelofibrosis	8 (23%)	1 (25%)	15 (31%)
Sternal, myelofibrosis			2 (4%)
Lymph node	(33)	(12)	(46)
Mesenteric, hematopoietic cell proliferation	1 (3%)	3 (25%)	2 (4%)
Mesenteric, hemorrhage			1 (2%)
Lymph node, mandibular	(33)	(4)	(45)
Angiectasis			1 (2%)
Depletion lymphoid	1 (3%)		
Hyperplasia			1 (2%)
Hyperplasia, lymphoid			3 (7%)
Spleen	(33)	(13)	(47)
Atrophy			1 (2%)
Depletion lymphoid	2 (6%)	1 (8%)	
Hematocyst			1 (2%)
Hyperplasia, lymphoid			1 (2%)
Red pulp, hematopoietic cell proliferation, diffuse	2 (6%)	4 (31%)	11 (23%)
INTEGUMENTARY SYSTEM			
Mammary gland	(30)	(3)	(34)
Hyperplasia, cystic	7 (23%)		20 (59%)
Skin	(33)	(5)	(48)
Acanthosis	1 (3%)		
Ulcer	1 (3%)		1 (2%)
Subcutaneous tissue, inflammation, chronic active	1 (3%)		1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(33)	(4)	(49)
Compression			2 (4%)
Meninges, infiltration cellular, lymphocytic	2 (6%)		3 (6%)
RESPIRATORY SYSTEM			
Lung	(35)	(5)	(50)
Hyperplasia, lymphoid			1 (2%)
Alveolar epithelium, hyperplasia			2 (4%)
Perivascular, infiltration cellular, lymphocytic			1 (2%)
Nose	(35)	(4)	(49)
Lumen, foreign body	1 (3%)		
SPECIAL SENSES SYSTEM			
Harderian gland	(32)	(4)	(49)
Inflammation, chronic active			1 (2%)
URINARY SYSTEM			
Kidney	(33)	(7)	(49)
Hyperplasia, lymphoid			2 (4%)
Inflammation, chronic active, multifocal		1 (14%)	
Metaplasia, osseous			2 (4%)
Nephropathy, chronic	13 (39%)		13 (27%)
Glomerulus, amyloid deposition	1 (3%)		
Renal tubule, cytoplasmic alteration, diffuse		1 (14%)	1 (2%)
Renal tubule, necrosis, acute			1 (2%)
Urinary bladder	(32)	(3)	(47)
Hyperplasia, lymphoid			1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Untreated Control	Low Dose	Mid Dose	High Dose
Animals initially in study	35	50	50	50
Animals removed	35	50	50	50
Animals examined histopathologically	35	50	50	49
ALIMENTARY SYSTEM				
Intestine small, jejunum	(32)	*(50)	*(50)	(47)
Peyer's patch, lymphoma malignant mixed				1 (2%)
Liver	(35)	(48)	(48)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)		
Hemangioma	1 (3%)		1 (2%)	1 (2%)
Hemangioma, multiple				1 (2%)
Hemangiosarcoma		1 (2%)	2 (4%)	2 (4%)
Hemangiosarcoma, multiple		2 (4%)		1 (2%)
Hepatocellular carcinoma	1 (3%)	6 (13%)	6 (13%)	8 (16%)
Hepatocellular carcinoma, multiple		1 (2%)	1 (2%)	1 (2%)
Hepatocellular adenoma	5 (14%)	10 (21%)	9 (19%)	10 (20%)
Hepatocellular adenoma, multiple		3 (6%)	8 (17%)	22 (45%)
Lymphoma malignant histiocytic	1 (3%)	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (3%)			
Lymphoma malignant mixed	1 (3%)		1 (2%)	1 (2%)
Pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)
Pancreas	(34)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (3%)			
Salivary glands	(35)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (3%)			
Lymphoma malignant mixed	1 (3%)			
Stomach, glandular	(33)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (3%)			
CARDIOVASCULAR SYSTEM				
Heart	(35)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic	1 (3%)			
Lymphoma malignant lymphocytic	1 (3%)			
ENDOCRINE SYSTEM				
Adrenal gland	(34)	(48)	(49)	(49)
Capsule, adenoma		1 (2%)		
Capsule, lymphoma malignant mixed	1 (3%)			
Adrenal gland, cortex	(34)	(48)	(48)	(49)
Adenoma	1 (3%)			
Adrenal gland, medulla	(34)	(48)	(48)	(49)
Pheochromocytoma malignant	1 (3%)			2 (4%)
Pheochromocytoma benign		4 (8%)	4 (8%)	5 (10%)
Bilateral, pheochromocytoma malignant				1 (2%)
Bilateral, pheochromocytoma benign			17 (35%)	39 (80%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(35)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (3%)			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM				
Bone marrow	(35)	*(50)	*(50)	(49)
Femoral, lymphoma malignant histiocytic			1 (2%)	
Femoral, lymphoma malignant lymphocytic	1 (3%)			
Lymph node	(31)	*(50)	*(50)	(47)
Bronchial, lymphoma malignant lymphocytic	1 (3%)			
Lumbar, lymphoma malignant mixed	2 (6%)		2 (4%)	
Mediastinal, lymphoma malignant histiocytic	1 (3%)			
Mediastinal, lymphoma malignant mixed	2 (6%)			2 (4%)
Mesenteric, lymphoma malignant histiocytic	1 (3%)		1 (2%)	
Mesenteric, lymphoma malignant mixed	1 (3%)	1 (2%)	2 (4%)	3 (6%)
Pancreatic, lymphoma malignant mixed				1 (2%)
Renal, lymphoma malignant mixed	1 (3%)		2 (4%)	
Lymph node, mandibular	(31)	*(50)	*(50)	(47)
Lymphoma malignant histiocytic	1 (3%)		1 (2%)	
Lymphoma malignant lymphocytic	3 (10%)			
Lymphoma malignant mixed	2 (6%)			2 (4%)
Spleen	(34)	*(50)	*(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)	
Hemangiosarcoma, multiple		1 (2%)		
Lymphoma malignant histiocytic	1 (3%)	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic	3 (9%)			
Lymphoma malignant mixed	2 (6%)	2 (4%)	3 (6%)	3 (6%)
Thymus	(21)	*(50)	*(50)	(27)
Lymphoma malignant mixed	1 (5%)			
INTEGUMENTARY SYSTEM				
Skin	(34)	*(50)	*(50)	(49)
Papilloma, multiple		1 (2%)		
Papilloma squamous				1 (2%)
Sebaceous gland, carcinoma		1 (2%)		
Subcutaneous tissue, fibroma		2 (4%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	4 (12%)	4 (8%)	6 (12%)	6 (12%)
Subcutaneous tissue, fibrosarcoma, multiple		2 (4%)		
Subcutaneous tissue, sarcoma				1 (2%)
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(35)	*(50)	*(50)	*(49)
Intercostal, fibrosarcoma, metastatic, skin		1 (2%)		
NERVOUS SYSTEM				
None				
RESPIRATORY SYSTEM				
Lung	(35)	*(50)	*(50)	(49)
Alveolar/bronchiolar adenoma	5 (14%)	1 (2%)	1 (2%)	4 (8%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Fibrosarcoma, metastatic, skin	1 (3%)		1 (2%)	
Hepatocellular carcinoma, metastatic				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Lymphoma malignant histiocytic	1 (3%)		1 (2%)	
Lymphoma malignant lymphocytic	1 (3%)			
Lymphoma malignant mixed	1 (3%)			
Pheochromocytoma malignant, metastatic, adrenal gland	1 (3%)			2 (4%)
Interstitium, mediastinum, fibrosarcoma, metastatic, multiple, skin		1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
SPECIAL SENSES SYSTEM				
Harderian gland	*(35)	*(50)	*(50)	*(49)
Adenoma	2 (6%)	1 (2%)		3 (6%)
URINARY SYSTEM				
Kidney	(35)	*(50)	*(50)	(49)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (3%)			
Lymphoma malignant mixed	2 (6%)			2 (4%)
Renal tubule, adenoma			1 (2%)	1 (2%)
Urinary bladder	(33)	*(50)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (3%)			
SYSTEMIC LESIONS				
Multiple organs	*(35)	*(50)	*(50)	*(49)
Hemangioma	1 (3%)		1 (2%)	2 (4%)
Lymphoma malignant mixed	2 (6%)	2 (4%)	3 (6%)	3 (6%)
Lymphoma malignant lymphocytic	3 (9%)			
Lymphoma malignant histiocytic	1 (3%)	2 (4%)	1 (2%)	2 (4%)
Hemangiosarcoma		4 (8%)	2 (4%)	3 (6%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	35	50	50	50
Terminal sacrifice	25	28	29	35
Moribund sacrifice	2	3	4	6
Natural death	8	19	17	9
TUMOR SUMMARY				
Total animals with primary neoplasms **	20	32	33	46
Total primary neoplasms	26	45	62	116
Total animals with benign neoplasms	11	21	28	45
Total benign neoplasms	14	23	42	89
Total animals with malignant neoplasms	10	22	16	22
Total malignant neoplasms	12	22	20	27
Total animals with secondary neoplasms ***	2	2	1	3
Total secondary neoplasms	2	3	1	5

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: UNTREATED CONTROL

WEEKS ON STUDY	029	032	065	067	068	072	076	098	101	102	104	104	104	104	104	104	104	104	104	105	105	105	105	105
CARCASS ID	251	221	061	271	241	081	301	171	281	231	021	051	131	211	351	011	201	311	321	031	071	091	101	111	141
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	M	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	M	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	M	+	M	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									
Hepatocellular carcinoma																									
Hepatocellular adenoma																	X								
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																									
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																						X			
Stomach	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic													X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, lymphoma malignant mixed																									
Adrenal gland, cortex	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Adrenal gland, medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	M
Pituitary gland	+	+	+	M	M	M	+	+	+	+	+	+	I	+	+	+	+	+	+	M	+	+	+	M	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Penis	+	+	+			+	+																		
Preputial gland			+			+	+																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Seminal vesicle														+											
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105		TOTAL: TISSUES TUMORS
CARCASS ID	151	161	191	291	331	341	041	121	181	261	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	35
Gallbladder	+	+	+	+	+	+	+	+	+	+	30
Intestine large	+	+	+	+	+	+	+	+	+	+	34
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	32
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	34
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	31
Intestine small	+	+	+	+	+	+	+	+	+	+	33
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	31
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	30
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	+	+	+	35
Hemangioma											1
Hepatocellular carcinoma							X				1
Hepatocellular adenoma	X	X		X					X		5
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed							X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant lymphocytic											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed											1
Stomach	+	+	+	+	+	+	+	+	+	+	33
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	33
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant lymphocytic											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic											1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	34
Capsule, lymphoma malignant mixed							X				1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	34
Adenoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	34
Pheochromocytoma malignant										X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	34
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	35
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant lymphocytic											1
Penis										+	6
Preputial gland											3
Prostate	+	+	+	+	+	+	+	+	+	+	34
Seminal vesicle											1
Testes	+	+	+	+	+	+	+	+	+	+	35

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	029	032	065	067	068	072	076	098	101	102	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105
CARCASS ID	251	221	061	271	241	081	301	171	281	231	021	051	131	211	351	011	201	311	321	031	071	091	101	111	141
HEMATOPOIETIC SYSTEM																									
Blood											+													+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, lymphoma malignant lymphocytic													X												
Lymph node	+	+	M	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Bronchial, lymphoma malignant lymphocytic																									
Lumbar, lymphoma malignant mixed																						X			
Mediastinal, lymphoma malignant histiocytic										X															
Mediastinal, lymphoma malignant mixed																						X			
Mesenteric, lymphoma malignant histiocytic										X															
Mesenteric, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	M	I	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic													X		X										
Lymphoma malignant mixed																						X			
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic													X		X										
Lymphoma malignant mixed																						X			
Thymus	+	M	+	M	M	M	M	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																						X			
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	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X	X		X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X	X	X								X			X		
Fibrosarcoma, metastatic, skin											X														
Lymphoma malignant histiocytic										X															
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																						X			
Pheochromocytoma malignant, metastatic, adrenal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																	X			X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																						X			
Urethra	+		+				+																		
Urinary bladder	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	1511	1611	1911	2911	3331	3441	0411	1211	1811	2611	
HEMATOPOIETIC SYSTEM											
Blood			+								3
Bone marrow	+	+	+	+	+	+	+	+	+	+	35
Femoral, lymphoma malignant lymphocytic											1
Lymph node	+	+	+	+	+	+	+	+	+	+	31
Bronchial, lymphoma malignant lymphocytic										X	1
Lumbar, lymphoma malignant mixed							X				2
Mediastinal, lymphoma malignant histiocytic											1
Mediastinal, lymphoma malign. mixed							X				2
Mesenteric, lymphoma malignant histiocytic											1
Mesenteric, lymphoma malign. mixed							X				1
Renal, lymphoma malignant mixed							X				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	31
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic										X	3
Lymphoma malignant mixed							X				2
Spleen	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic										X	3
Lymphoma malignant mixed							X				2
Thymus	I	+	M	+	+	M	M	+		+	21
Lymphoma malignant mixed											1
INTEGUMENTARY SYSTEM											
Mammary gland	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	34
Subcutaneous tissue, fibrosarcoma			X								4
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	35
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	35
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	35
Alveolar/bronchiolar adenoma						X					5
Fibrosarcoma, metastatic, skin											1
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed											1
Pheochromocytoma malignant, metastatic, adrenal gland										X	1
Nose	+	+	+	+	+	+	+	+	+	+	35
Trachea	+	+	+	+	+	+	+	+	+	+	35
SPECIAL SENSES SYSTEM											
Harderian gland	M	M	+	M	+	+	+	M	+	+	27
Adenoma											2
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed							X				2
Urethra											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant lymphocytic											1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF OF PENTACHLOROPHENOL, DOWICIDE EC-7: LOW DOSE

WEEKS ON STUDY	0 0 9	0 3 7	0 4 4	0 6 2	0 6 3	0 6 9	0 7 0	0 7 4	0 7 6	0 8 2	0 8 8	0 8 8	0 8 8	0 8 8	0 9 4	0 9 5	0 9 5	0 9 9	1 0 0	1 0 0	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	8 1 1	4 5 1	6 9 1	7 2 1	7 4 1	4 4 1	9 2 1	6 3 1	7 5 1	6 4 1	5 3 1	6 8 1	7 6 1	4 6 1	5 5 1	4 8 1	6 0 1	7 0 1	4 3 1	8 8 1	5 6 1	7 8 1	4 7 1	6 5 1	7 3 1
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	+	+	A	+	+	+	+	+		+	+											
Gallbladder	+	A	+	A	A	A	A	A	+	+	+		A	A											
Intestine large	A	+	+	+	+	A	+	A	+	+	+		+	+											
Intestine large, cecum	A	M	+	A	M	A	A	A	+	+	+		+	M											
Intestine large, colon	A	+	+	+	+	A	+	A	+	+	+		+	+											
Intestine large, rectum	A	M	+	A	+	A	+	A	+	M	+		+	A											
Intestine small	A	+	+	A	M	A	A	A	+	+	+		+	+											
Intestine small, duodenum	A	A	+	A	M	A	A	A	+		+		+	+											
Intestine small, ileum	A	+	+	A	M	A	A	A	+		+		+	+											
Intestine small, jejunum	A	+	+	A	M	A	A	A	+		+		+	+											
Liver	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									X
Hemangiosarcoma																									
Hemangiosarcoma, multiple															X										
Hepatocellular carcinoma													X			X			X			X			
Hepatocellular carcinoma, multiple																	X								
Hepatocellular adenoma																					X	X			
Hepatocellular adenoma, multiple														X											
Lymphoma malignant histiocytic																		X		X					
Pancreas	+	+	+	+	+	A	+	A	+	+	+		+	+											
Salivary glands	+	M	+	+	+	A	+	+	+	+	+		+	+											
Stomach	+	+	+	+	+	A	+	A	+	+	+		+	+											
Stomach, forestomach	+	+	+	+	+	A	+	A	+	+	+		+	+											
Stomach, glandular	+	+	+	+	+	A	+	A	+	+	+		+	+											
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+		+	+											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	A	+	A	+	+	+		+	+											
Parathyroid gland	+	M	+	+	+	A	+	+	+	+	+		+	M											
Pituitary gland	+	M	+	+	M	M	+	M	+	+	+		+	+											
Thyroid gland	+	M	+	+	+	A	+	+	+	+	+		+	+											
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+		+	+											
Penis												+													
Preputial gland			+			+				+		+													
Prostate	+	+	+	+	+	A	+	A	+	+	+		+	+											
Seminal vesicle			+					+																	
Testes	+	+	+	+	+	+	+	A	+	+	+		+	+											

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	801	841	861	871	911	501	511	521	581	591	661	771	831	891	901	491	571	621	671	711	851	541	611	791	821	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										11
Gallbladder																										5
Intestine large																										10
Intestine large, cecum																										5
Intestine large, colon																										10
Intestine large, rectum																										6
Intestine small																										7
Intestine small, duodenum																										5
Intestine small, ileum																										6
Intestine small, jejunum																										6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma																								X		1
Hemangiosarcoma, multiple								X																		2
Hepatocellular carcinoma														X					X							6
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X				X						X	X	X			X							X		X	10
Hepatocellular adenoma, multiple										X								X								3
Lymphoma malignant histiocytic																										2
Pancreas															+											12
Salivary glands																										11
Stomach																										11
Stomach, forestomach																										11
Stomach, glandular																										11
CARDIOVASCULAR SYSTEM																										
Heart																										13
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Capsule, adenoma							X																			1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign														X							X			X		4
Islets, pancreatic																										11
Parathyroid gland																										10
Pituitary gland																										9
Thyroid gland																										11
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																										13
Penis							+	+											+	+			+			6
Preputial gland					+															+			+		+	8
Prostate																										11
Seminal vesicle								+																		3
Testes																										12

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	009	037	044	062	063	069	070	074	076	082	088	088	088	088	094	095	095	099	100	100	101	104	104	104	104
CARCASS ID	811	451	691	721	741	441	921	631	751	641	531	681	761	461	551	481	601	701	431	881	561	781	471	651	731
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	A	A	A	+	+	+		+	+											
Lymph node	+	M	M	+	+	A	+	+	+	M	+	+	+	M							+				
Mesenteric, lymphoma malignant mixed																									
Lymph node, mandibular	+	M	M	+	+	A	+	+	+	M	+		+	M											
Spleen	+	+	+	+	+	A	+	A	+	+	+		+	+						+	+				+
Hemangiosarcoma																									
Hemangiosarcoma, multiple																									
Lymphoma malignant histiocytic																				X					
Lymphoma malignant mixed																									
Thymus	+	M	+	+	M	M	M	A	+	M	M		+	M											
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M		M	M											
Skin	+	+	+	+	+	A	+	+	+	+	+		+	+					+		+		+	+	+
Papilloma, multiple																									
Sebaceous gland, carcinoma																					X				
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma														X									X		
Subcutaneous tissue, fibrosarcoma, multiple																									X
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+			+		+
Skeletal muscle																									
Intercostal, fibrosarcoma, metastatic, skin																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	A	+	+	+	+	+		+	+											
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+		+	+											
Alveolar/bronchiolar adenoma													X												
Interstitium, mediastinum, fibrosarcoma, metastatic, multiple, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+		+	+											
Trachea	+	M	+	+	+	A	+	+	+	+	+		+	+											
SPECIAL SENSES SYSTEM																									
Eye												+													
Harderian gland	+	M	+	+	+	+	+	A	+	+	+		+	+											
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	A	+	+	+		+	+			+								
Urethra				+				+																	
Urinary bladder	A	+	+	+	+	A	+	A	+	+	+	+	+	+											

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	801	841	861	871	911	501	511	521	581	591	661	771	831	891	901	491	571	621	671	711	851	541	611	791	821	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										10
Lymph node				+	+			+				+														14
Mesenteric, lymphoma malignant mixed												X														1
Lymph node, mandibular																										8
Spleen					+			+				+	+						+							19
Hemangiosarcoma					X																					1
Hemangiosarcoma, multiple								X																		1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed												X	X													2
Thymus																										5
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin		+	+	+	+	+		+	+			+			+	+	+	+			+	+	+			32
Papilloma, multiple		X																								1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma				X					X																	2
Subcutaneous tissue, fibrosarcoma						X												X								4
Subcutaneous tissue, fibrosarcoma, multiple																							X			2
MUSCULOSKELETAL SYSTEM																										
Bone	+		+	+		+		+		+			+	+	+	+	+	+			+	+	+	+	+	36
Skeletal muscle																							+			1
Intercostal, fibrosarcoma, metastatic, skin																							X			1
NERVOUS SYSTEM																										
Brain																										12
RESPIRATORY SYSTEM																										
Lung																						+	+			15
Alveolar/bronchiolar adenoma																										1
Interstitium, mediastinum, fibrosarcoma, metastatic, multiple, skin																							X			1
Nose																										13
Trachea																										11
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland																		+								12
Adenoma																		X								1
URINARY SYSTEM																										
Kidney																+	+									14
Urethra																										2
Urinary bladder																										11

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: MID DOSE

WEEKS ON STUDY	0 0 4	0 2 0	0 2 0	0 4 2	0 4 2	0 4 2	0 4 2	0 4 5	0 4 7	0 4 9	0 5 1	0 6 0	0 7 8	0 7 9	0 8 3	0 8 6	0 8 7	0 8 7	0 9 5	0 9 8	0 9 9	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	1 4 0 1	1 3 2 1	1 1 7 1	1 2 4 1	1 2 7 1	1 2 3 1	1 2 6 1	1 1 8 1	1 1 3 1	1 3 8 1	1 1 4 1	1 0 4 1	1 3 5 1	1 2 8 1	1 5 0 1	1 2 1 1	1 4 6 1	1 4 5 1	1 1 6 1	1 0 3 1	1 3 3 1	1 0 7 1	1 1 5 1	1 1 9 1	1 2 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	A	+	+							
Gallbladder	+	+	+	A	A	A	A	+	+	A	A	+	+	+	+	A	A	A							
Intestine large	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+							
Intestine large, cecum	M	+	M	+	A	A	A	+	+	+	A	+	+	M	+	A	+	M							
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+							
Intestine large, rectum	M	A	M	M	A	A	A	+	+	M	+	+	+	+	+	A	+	M							
Intestine small	+	+	M	+	+	A	A	+	+	+	+	+	+	+	+	A	+	M							
Intestine small, duodenum	+	+	M	+	+	A	A	+	+	+	A	A	+	+	+	A	+	M							
Intestine small, ileum	M	A	M	+	A	A	A	+	+	+	A	A	+	+	+	A	+	M							
Intestine small, jejunum	M	+	M	+	+	A	A	+	+	+	+	+	+	+	+	A	+	M							
Liver	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																					X			X	
Hepatocellular carcinoma																						X		X	
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																		X		X					
Hepatocellular adenoma, multiple																			X			X	X		X
Lymphoma malignant histiocytic													X												
Lymphoma malignant mixed																					X				
Pancreas	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	A	+	+							
Salivary glands	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	A	+	+							
Stomach	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+							
Stomach, forestomach	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+							
Stomach, glandular	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+							
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X	
Bilateral, pheochromocytoma benign																X			X			X	X		X
Islets, pancreatic	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	A	+	+							
Parathyroid gland	M	+	M	M	M	M	M	+	+	M	+	+	+	+	+	M	+	+							
Pituitary gland	+	+	+	+	+	I	M	+	+	M	+	+	+	+	+	M	+	+							
Thyroid gland	+	+	+	+	+	M	A	+	+	M	+	+	+	+	+	M	+	+							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Penis	+																								
Preputial gland								+				+													
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M							
Seminal vesicle	+																+								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE
(Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	1361	1391	1441	1471	1101	1371	1421	1491	1051	1091	1221	1291	1301	1311	1341	1411	1511	1061	1081	1111	1121	1201	1431	1481	1521	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										15
Gallbladder																										9
Intestine large																										16
Intestine large, cecum																										9
Intestine large, colon																										16
Intestine large, rectum																										8
Intestine small																										13
Intestine small, duodenum																										11
Intestine small, ileum																										8
Intestine small, jejunum																										12
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma														X												1
Hemangiosarcoma																										2
Hepatocellular carcinoma			X									X				X							X			6
Hepatocellular carcinoma, multiple									X																	1
Hepatocellular adenoma			X	X		X	X			X							X			X						9
Hepatocellular adenoma, multiple	X													X		X									X	8
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
Pancreas																										14
Salivary glands																										15
Stomach																										15
Stomach, forestomach																										15
Stomach, glandular																										15
CARDIOVASCULAR SYSTEM																										
Heart																										17
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign		X		X																			X			4
Bilateral, pheochromocytoma benign	X		X		X				X	X	X	X	X	X		X						X			X	17
Islets, pancreatic																										14
Parathyroid gland																+										11
Pituitary gland																										14
Thyroid gland																										14
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis																										18
Penis																										1
Preputial gland	+									+																4
Prostate																										15
Seminal vesicle																										2
Testes																										18

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	004	020	020	042	042	042	042	045	047	049	051	060	078	079	083	086	087	087	095	098	099	099	104	104	104	104
CARCASS ID	14001	13211	11171	12411	12271	12231	12261	11181	11131	13811	11141	10411	13511	12811	15011	12211	14611	14511	11161	10311	13311	13311	10711	11511	11911	12511
HEMATOPOIETIC SYSTEM																										
Blood																		+								
Bone marrow	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	A	+	+								
Femoral, lymphoma malignant histiocytic													X													
Lymph node	M	M	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+				+	+	+		
Lumbar, lymphoma malignant mixed																						X				
Mesenteric, lymphoma malignant histiocytic													X													
Mesenteric, lymphoma malignant mixed																						X				
Renal, lymphoma malignant mixed																						X				
Lymph node, mandibular	M	M	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+								
Lymphoma malignant histiocytic													X													
Spleen	+	+	+	+	+	A	A	+	+	M	+	+	+	+	+	A	+	+				+			+	
Hemangiosarcoma																									X	
Lymphoma malignant histiocytic													X													
Lymphoma malignant mixed																						X				
Thymus	+	+	M	+	+	M	A	+	+	M	+	+	+	M	+	M	M	+								
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M								
Skin	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	A	+	+		+					+	
Subcutaneous tissue, fibroma																									X	
Subcutaneous tissue, fibrosarcoma															X		X	X								
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+				+	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+								
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+						+		
Alveolar/bronchiolar adenoma																								X		
Alveolar/bronchiolar carcinoma																										
Fibrosarcoma, metastatic, skin																		X								
Lymphoma malignant histiocytic													X													
Nose	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Trachea	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	A	+	+								
SPECIAL SENSES SYSTEM																										
Harderian gland	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+								
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+								
Renal tubule, adenoma																										
Urethra					+				+		+	+														
Urinary bladder	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	A				+				

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	13361	13991	14401	14771	11011	13771	14211	14491	10511	10911	12211	12911	13011	13111	13411	14111	15111	10611	10811	11111	11211	12011	14431	14811	15211	
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow																										14
Femoral, lymphoma malignant histiocytic																										1
Lymph node	+		+	+							+				+								+			22
Lumbar, lymphoma malignant mixed															X											2
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malign. mixed															X											2
Renal, lymphoma malignant mixed															X											2
Lymph node, mandibular																										13
Lymphoma malignant histiocytic																										1
Spleen						+									+								+		+	20
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed															X								X			3
Thymus																										11
INTEGUMENTARY SYSTEM																										
Mammary gland																										
Skin		+	+			+					+				+							+		+	+	26
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma			X			X															X					6
MUSCULOSKELETAL SYSTEM																										
Bone			+	+							+			+			+		+				+		+	29
NERVOUS SYSTEM																										
Brain																										16
RESPIRATORY SYSTEM																										
Lung											+															19
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma											X															1
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant histiocytic																										1
Nose																										16
Trachea																										15
SPECIAL SENSES SYSTEM																										
Harderian gland																										13
URINARY SYSTEM																										
Kidney															+						+				+	20
Renal tubule, adenoma																					X					1
Urethra																										4
Urinary bladder																										15

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: HIGH DOSE

WEEKS ON STUDY	0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1
	0 3 5 5 6 7 8 8 8 8 9 9 0 0 2 3 4 4 4 4 4 4 4 4 4 4
	9 7 3 5 6 7 7 7 7 8 1 8 0 2 3 4 4 4 4 4 4 4 4 4 4 4
CARCASS ID	1 1 1 2 1 1 1 1 1 1 1 1 1 1 2 1 1 1 2 2 1 1 1 1 1
	7 9 6 0 9 8 6 6 8 9 7 9 8 9 1 6 6 9 8 0 9 7 7 8 8 8
	2 2 8 5 6 8 4 3 7 5 6 9 9 1 2 5 9 8 1 6 9 5 9 0 1 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 1
ALIMENTARY SYSTEM	
Esophagus	+ +
Gallbladder	+ + + A A +
Intestine large	+ +
Intestine large, cecum	M + + + + + + + + + M + + + + + + + + + + + + + +
Intestine large, colon	+ +
Intestine large, rectum	+ + + M M +
Intestine small	+ +
Intestine small, duodenum	+ M + + M +
Intestine small, ileum	M + + M + + + + + + A + + + + + + + + + + + + + +
Intestine small, jejunum	A + + M +
Peyer's patch, lymphoma malignant mixed	
Liver	+ +
Hemangioma	
Hemangioma, multiple	X
Hemangiosarcoma	
Hemangiosarcoma, multiple	X
Hepatocellular carcinoma	X X
Hepatocellular carcinoma, multiple	X
Hepatocellular adenoma	X X X
Hepatocellular adenoma, multiple	X X X X X
Lymphoma malignant histiocytic	X X
Lymphoma malignant mixed	
Pheochromocytoma malignant, metastatic, adrenal gland	
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tooth	+
CARDIOVASCULAR SYSTEM	
Heart	+ +
ENDOCRINE SYSTEM	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	+ +
Pheochromocytoma malignant	
Pheochromocytoma benign	X X
Bilateral, pheochromocytoma malignant	
Bilateral, pheochromocytoma benign	X X X X X X X X X X X X X X X X X X X X X X X X
Islets, pancreatic	+ +
Parathyroid gland	M + + + + + + + + + + + M + + M + + + + M + + + + +
Pituitary gland	M + + M + + + M + M + + + + + + + + + + + M + M + +
Thyroid gland	+ +
GENERAL BODY SYSTEM	
None	
GENITAL SYSTEM	
Epididymis	+ +
Penis	
Preputial gland	+
Prostate	+ +
Seminal vesicle	+
Testes	+ +

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	18311	18411	18511	19411	20011	20031	20071	16711	17011	17411	19011	19311	19711	21011	16611	17111	17311	17711	17811	18611	20011	20021	20411	20811	21111	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peyer's patch, lymphoma malignant mixed			X																							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma				X																						1
Hemangioma, multiple																										1
Hemangiosarcoma												X	X													2
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma	X	X		X			X			X												X				8
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X	X	X			X	X		X				X												10
Hepatocellular adenoma, multiple	X				X				X		X	X	X		X	X	X		X	X	X	X	X	X	X	22
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed														X												1
Pheochromocytoma malignant, metastatic, adrenal gland																				X						1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																							+			3
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant										X										X						2
Pheochromocytoma benign										X				X						X						5
Bilateral, pheochromocytoma malignant															X											1
Bilateral, pheochromocytoma benign	X	X	X	X	X	X	X	X	X		X	X	X			X	X	X	X		X	X	X	X	X	39
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	M	+	I	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	38
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis			+		+		+																+			4
Preputial gland					+		+											+								4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	009	037	053	055	066	077	087	087	087	088	091	098	100	102	103	104	104	104	104	104	104	104	104	104	104
CARCASS ID	17201	19201	16881	20551	19061	18881	16441	16311	18711	19551	17611	19991	18911	19111	21211	16551	16991	19881	20061	20091	17551	17791	18001	18111	18211
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	M	+	+	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant mixed																									
Pancreatic, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	M	+	+	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Thymus	M	+	+	M	+	M	+		M	+	M	M	M	+	M	+	M	M	M	+	+	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M		M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma														X											
Subcutaneous tissue, fibrosarcoma				X		X				X			X		X										
Subcutaneous tissue, sarcoma											X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar adenoma, multiple																									
Hepatocellular carcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic																									
Pheochromocytoma malignant, metastatic, adrenal gland																									
Nose	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland	M	M	+	M	+	+	+		+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	M
Adenoma							X																		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																		X							
Lymphoma malignant mixed																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	18311	18411	18511	19411	20111	20031	20071	16711	17011	17411	19011	19311	19711	21011	16611	17111	17311	17711	17811	18611	20001	20021	20041	20081	21111	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mediastinal, lymphoma malign. mixed		X												X												2
Mesenteric, lymphoma malignant mixed		X	X											X												3
Pancreatic, lymphoma malignant mixed		X																								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant mixed			X											X												2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed		X	X											X												3
Thymus	M	M	M	+	+	M	+	M	M	+	+	+	M	+	M	+	M	+	+	+	+	+	M	+	+	27
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous									X																	1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma															X											6
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma							X													X			X			4
Alveolar/bronchiolar adenoma, multiple	X																									1
Hepatocellular carcinoma, metastatic, liver										X																1
Hepatocellular carcinoma, metastatic	X																									1
Pheochromocytoma malignant, metastatic, adrenal gland										X										X						2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye									+																	1
Harderian gland	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	M	M	+	+	35
Adenoma							X		X																	3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed		X												X												2
Renal tubule, adenoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Control	100 ppm	200 ppm	600 ppm
Adrenal Gland/Medulla: Pheochromocytoma				
Overall Rates (a)	0/34 (0%)	4/48 (8%)	21/48 (44%)	44/49 (90%)
Adjusted Rates (b)	0.0%	13.8%	67.5%	97.8%
Terminal Rates (c)	0/25 (0%)	3/28 (11%)	19/29 (66%)	34/35 (97%)
Day of First Observation		723	598	458
Life Table Tests (d)	P<0.001	P=0.081	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.107	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.111	P<0.001	P<0.001
Adrenal Gland/Medulla: Malignant Pheochromocytoma				
Overall Rates (a)	1/34 (3%)	0/48 (0%)	0/48 (0%)	3/49 (6%)
Adjusted Rates (b)	4.0%	0.0%	0.0%	8.6%
Terminal Rates (c)	1/25 (4%)	0/28 (0%)	0/29 (0%)	3/35 (9%)
Day of First Observation	727			727
Life Table Tests (d)	P=0.104	P=0.477N	P=0.470N	P=0.431
Logistic Regression Tests (d)	P=0.104	P=0.477N	P=0.470N	P=0.431
Cochran-Armitage Trend Test (d)	P=0.084			
Fisher Exact Test (d)		P=0.415N	P=0.415N	P=0.456
Adrenal Gland/Medulla: Pheochromocytoma or Malignant Pheochromocytoma				
Overall Rates (a)	1/34 (3%)	4/48 (8%)	21/48 (44%)	45/49 (92%)
Adjusted Rates (b)	4.0%	13.8%	67.5%	100.0%
Terminal Rates (c)	1/25 (4%)	3/28 (11%)	19/29 (66%)	35/35 (100%)
Day of First Observation	727	723	598	458
Life Table Tests (d)	P<0.001	P=0.218	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.268	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.305	P<0.001	P<0.001
Harderian Gland: Adenoma				
Overall Rates (a)	2/35 (6%)	1/50 (2%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	8.0%	3.6%	0.0%	7.9%
Terminal Rates (c)	2/25 (8%)	1/28 (4%)	0/29 (0%)	2/35 (6%)
Day of First Observation	727	727		604
Life Table Tests (d)	P=0.375	P=0.460N	P=0.206N	P=0.658
Logistic Regression Tests (d)	P=0.354	P=0.460N	P=0.206N	P=0.660
Cochran-Armitage Trend Test (d)	P=0.322			
Fisher Exact Test (d)		P=0.367N	P=0.167N	P=0.657
Liver: Hepatocellular Adenoma				
Overall Rates (a)	5/35 (14%)	13/48 (27%)	17/48 (35%)	32/49 (65%)
Adjusted Rates (b)	20.0%	41.6%	53.0%	84.1%
Terminal Rates (c)	5/25 (20%)	10/28 (36%)	14/29 (48%)	29/35 (83%)
Day of First Observation	727	613	608	536
Life Table Tests (d)	P<0.001	P=0.057	P=0.008	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.083	P=0.007	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.129	P=0.027	P<0.001
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	1/35 (3%)	7/48 (15%)	7/48 (15%)	9/49 (18%)
Adjusted Rates (b)	4.0%	20.2%	24.1%	25.0%
Terminal Rates (c)	1/25 (4%)	2/28 (7%)	7/29 (24%)	8/35 (23%)
Day of First Observation	727	612	727	717
Life Table Tests (d)	P=0.127	P=0.062	P=0.047	P=0.034
Logistic Regression Tests (d)	P=0.108	P=0.075	P=0.047	P=0.033
Cochran-Armitage Trend Test (d)	P=0.080			
Fisher Exact Test (d)		P=0.075	P=0.075	P=0.029

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Control	100 ppm	200 ppm	600 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	6/35 (17%)	19/48 (40%)	21/48 (44%)	34/49 (69%)
Adjusted Rates (b)	24.0%	53.8%	65.5%	87.1%
Terminal Rates (c)	6/25 (24%)	12/28 (43%)	18/29 (62%)	30/35 (86%)
Day of First Observation	727	612	608	536
Life Table Tests (d)	P<0.001	P=0.009	P=0.002	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.015	P=0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.024	P=0.009	P<0.001
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/35 (14%)	(e) 1/15 (7%)	(e,f) 1/19 (5%)	5/49 (10%)
Adjusted Rates (b)	19.2%			14.3%
Terminal Rates (c)	4/25 (16%)			5/35 (14%)
Day of First Observation	710			727
Life Table Test (d)				P=0.409N
Logistic Regression Test (d)				P=0.413N
Fisher Exact Test (d)				P=0.405N
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	4/35 (11%)	6/50 (12%)	6/50 (12%)	6/49 (12%)
Adjusted Rates (b)	14.6%	20.1%	18.0%	14.2%
Terminal Rates (c)	2/25 (8%)	5/28 (18%)	3/29 (10%)	1/35 (3%)
Day of First Observation	681	613	578	379
Life Table Tests (d)	P=0.523N	P=0.456	P=0.469	P=0.593
Logistic Regression Tests (d)	P=0.564	P=0.554	P=0.527	P=0.586
Cochran-Armitage Trend Test (d)	P=0.543			
Fisher Exact Test (d)		P=0.608	P=0.608	P=0.595
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	4/35 (11%)	8/50 (16%)	7/50 (14%)	7/49 (14%)
Adjusted Rates (b)	14.6%	27.0%	21.1%	16.5%
Terminal Rates (c)	2/25 (8%)	7/28 (25%)	4/29 (14%)	1/35 (3%)
Day of First Observation	681	613	578	379
Life Table Tests (d)	P=0.516N	P=0.248	P=0.359	P=0.491
Logistic Regression Tests (d)	P=0.558	P=0.327	P=0.405	P=0.476
Cochran-Armitage Trend Test (d)	P=0.528			
Fisher Exact Test (d)		P=0.396	P=0.498	P=0.484
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (a)	4/35 (11%)	8/50 (16%)	7/50 (14%)	8/49 (16%)
Adjusted Rates (b)	14.6%	27.0%	21.1%	18.6%
Terminal Rates (c)	2/25 (8%)	7/28 (25%)	4/29 (14%)	1/35 (3%)
Day of First Observation	681	613	578	379
Life Table Tests (d)	P=0.501	P=0.248	P=0.359	P=0.396
Logistic Regression Tests (d)	P=0.427	P=0.327	P=0.405	P=0.373
Cochran-Armitage Trend Test (d)	P=0.397			
Fisher Exact Test (d)		P=0.396	P=0.498	P=0.381
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	0/35 (0%)	(g) 4/50 (8%)	(h) 2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	13.2%	6.7%	8.6%
Terminal Rates (c)	0/25 (0%)	3/28 (11%)	1/29 (3%)	3/35 (9%)
Day of First Observation		655	690	727
Life Table Tests (d)	P=0.425	P=0.084	P=0.268	P=0.186
Logistic Regression Tests (d)	P=0.411	P=0.101	P=0.277	P=0.186
Cochran-Armitage Trend Test (d)	P=0.365			
Fisher Exact Test (d)		P=0.114	P=0.343	P=0.193

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Control	100 ppm	200 ppm	600 ppm
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (a)	1/35 (3%)	(g) 4/50 (8%)	(h) 3/50 (6%)	5/49 (10%)
Adjusted Rates (b)	4.0%	13.2%	10.0%	14.3%
Terminal Rates (c)	1/25 (4%)	3/28 (11%)	2/29 (7%)	5/35 (14%)
Day of First Observation	727	655	690	727
Life Table Tests (d)	P=0.264	P=0.224	P=0.356	P=0.193
Logistic Regression Tests (d)	P=0.250	P=0.264	P=0.361	P=0.193
Cochran-Armitage Trend Test (d)	P=0.200			
Fisher Exact Test (d)		P=0.310	P=0.453	P=0.199
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	6/35 (17%)	(g) 4/50 (8%)	(h) 4/50 (8%)	5/49 (10%)
Adjusted Rates (b)	23.1%	12.9%	12.4%	13.5%
Terminal Rates (c)	5/25 (20%)	2/28 (7%)	2/29 (7%)	4/35 (11%)
Day of First Observation	710	690	541	608
Life Table Tests (d)	P=0.345N	P=0.296N	P=0.278N	P=0.271N
Logistic Regression Tests (d)	P=0.372N	P=0.226N	P=0.248N	P=0.257N
Cochran-Armitage Trend Test (d)	P=0.422N			
Fisher Exact Test (d)		P=0.172N	P=0.172N	P=0.272N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Incomplete sampling of tissues
(f) One carcinoma was also observed.
(g) Nineteen spleens were examined microscopically.
(h) Twenty spleens were examined microscopically.

TABLE C4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	7/50	14/50	19/50
N-Phenyl-2-naphthylamine	6/47	6/47	11/47
C.I. Disperse Yellow 3	7/50	14/50	20/50
D & C Red No. 9	4/50	4/50	8/50
C.I. Solvent Yellow 14	5/49	10/49	15/49
Rotenone	7/47	6/47	12/47
L-Ascorbic acid	6/50	10/50	16/50
TOTAL	42/343 (12.2%)	64/343 (18.7%)	101/343 (29.4%)
SD (b)	2.44%	7.77%	8.42%
Range (c)			
High	7/47	14/50	20/50
Low	4/50	4/50	8/50
Overall Historical Incidence			
TOTAL	259/2,032 (12.7%)	379/2,032 (18.7%)	609/2,032 (30.0%)
SD (b)	7.21%	6.50%	7.59%
Range (c)			
High	22/50	15/50	29/50
Low	0/49	4/50	8/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence of Pheochromocytomas in Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	1/46
N-Phenyl-2-naphthylamine	0/48
C.I. Disperse Yellow 3	1/50
D & C Red No. 9	0/49
C.I. Solvent Yellow 14	0/48
Rotenone	0/47
L-Ascorbic acid	0/50
TOTAL	2/338 (0.6%)
SD (b)	1.02%
Range (c)	
High	1/46
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 30/1,969 (1.5%)
SD (b)	2.11%
Range (c)	
High	4/49
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two malignant pheochromocytomas

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Untreated Control	Low Dose	Mid Dose	High Dose
Animals initially in study	35	50	50	50
Animals removed	35	50	50	50
Animals examined histopathologically	35	50	50	49
ALIMENTARY SYSTEM				
Intestine large, rectum	(31)	(6)	(8)	(47)
Prolapse				1 (2%)
Liver	(35)	(48)	(48)	(49)
Basophilic focus	1 (3%)	3 (6%)		2 (4%)
Clear cell focus		2 (4%)		4 (8%)
Clear cell focus, multiple		17 (35%)	21 (44%)	15 (31%)
Degeneration, cystic		2 (4%)	1 (2%)	
Hematopoietic cell proliferation, diffuse		1 (2%)		
Hematopoietic cell proliferation, multifocal	1 (3%)	20 (42%)	16 (33%)	40 (82%)
Hyperplasia, focal		2 (4%)	3 (6%)	
Infarct	2 (6%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, acute	1 (3%)			
Inflammation, chronic active, diffuse		36 (75%)	44 (92%)	43 (88%)
Pigmentation, multifocal		40 (83%)	37 (77%)	45 (92%)
Thrombus, multiple		1 (2%)		
Bile canaliculi, hyperplasia, atypical, diffuse		1 (2%)		
Bile duct, cyst		2 (4%)	3 (6%)	1 (2%)
Bile duct, cyst, multifocal			2 (4%)	
Bile duct, cyst, multiple		2 (4%)		
Bile duct, hyperplasia, multifocal	1 (3%)	3 (6%)	5 (10%)	32 (65%)
Hepatocyte, cytomegaly, diffuse		48 (100%)	48 (100%)	47 (96%)
Hepatocyte, necrosis, acute, diffuse		47 (98%)	47 (98%)	46 (94%)
Hepatocyte, necrosis, acute, focal	1 (3%)			
Pancreas	(34)	(12)	(14)	(49)
Acinus, atrophy	2 (6%)	1 (8%)		
Acinus, degeneration				1 (2%)
Acinus, inflammation, chronic				1 (2%)
Duct, ectasia		1 (8%)		
Stomach, forestomach	(33)	(11)	(15)	(49)
Acanthosis		1 (9%)		2 (4%)
Hyperkeratosis		1 (9%)		
Inflammation, acute	1 (3%)			
Inflammation, chronic active				1 (2%)
Ulcer		1 (9%)		1 (2%)
Stomach, glandular	(33)	(11)	(15)	(49)
Dysplasia				3 (6%)
Ulcer, acute	1 (3%)			
Tooth				(3)
Developmental malformation				1 (33%)
Peridontal tissue, inflammation, chronic active				2 (67%)
CARDIOVASCULAR SYSTEM				
Heart	(35)	(13)	(17)	(49)
Degeneration, chronic			1 (6%)	
Mineralization	1 (3%)			
Atrium, thrombus			1 (6%)	2 (4%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM				
Adrenal gland	(34)	(48)	(49)	(49)
Capsule, ectopic tissue	3 (9%)			
Capsule, hyperplasia	30 (88%)	34 (71%)	34 (69%)	29 (59%)
Adrenal gland, cortex	(34)	(48)	(48)	(49)
Cyst	1 (3%)			
Cytoplasmic alteration		1 (2%)		
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	6 (18%)	7 (15%)	1 (2%)	1 (2%)
Hypertrophy	4 (12%)	3 (6%)	6 (13%)	1 (2%)
Adrenal gland, medulla	(34)	(48)	(48)	(49)
Hyperplasia	1 (3%)	19 (40%)	13 (27%)	1 (2%)
Pituitary gland	(29)	(9)	(14)	(38)
Pars distalis, cyst	1 (3%)			
Thyroid gland	(35)	(11)	(14)	(48)
Follicle, cyst	1 (3%)			
Follicular cell, hyperplasia	3 (9%)			2 (4%)
Follicular cell, hypertrophy		1 (9%)		
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(35)	(13)	(18)	(49)
Granuloma sperm				1 (2%)
Spermatocele		1 (8%)		
Penis	(6)	(6)	(1)	(4)
Inflammation, acute				1 (25%)
Inflammation, chronic active	3 (50%)	1 (17%)	1 (100%)	
Preputial gland	(3)	(8)	(4)	(4)
Dilatation		1 (13%)		
Hyperplasia		1 (13%)		
Inflammation, chronic active	1 (33%)	6 (75%)	4 (100%)	4 (100%)
Duct, dilatation	2 (67%)	2 (25%)		2 (50%)
Prostate	(34)	(11)	(15)	(49)
Inflammation, acute		1 (9%)	3 (20%)	
Inflammation, chronic active	1 (3%)	1 (9%)	1 (7%)	
Seminal vesicle	(1)	(3)	(2)	(1)
Dilatation		2 (67%)		
Inflammation, chronic active	1 (100%)	1 (33%)		
Testes	(35)	(12)	(18)	(49)
Inflammation, chronic active	1 (3%)			
Germinal epithelium, degeneration				1 (2%)
HEMATOPOIETIC SYSTEM				
Blood	(3)		(1)	
Neutrophilia	3 (100%)		1 (100%)	
Bone marrow	(35)	(10)	(14)	(49)
Femoral, hyperplasia, neutrophil	2 (6%)	1 (10%)	1 (7%)	
Femoral, hyperplasia, neutrophil, diffuse		1 (10%)		
Lymph node	(31)	(14)	(22)	(47)
Angiectasis		1 (7%)		
Hyperplasia, plasma cell		1 (7%)		
Lumbar, hyperplasia, lymphoid	1 (3%)			
Mesenteric, hematopoietic cell proliferation	5 (16%)	4 (29%)	10 (45%)	10 (21%)
Mesenteric, hematopoietic cell proliferation, multifocal	1 (3%)	1 (7%)		
Mesenteric, hyperplasia, lymphoid				1 (2%)
Pancreatic, inflammation, chronic active	1 (3%)			

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node, mandibular	(31)	(8)	(13)	(47)
Depletion lymphoid			1 (8%)	
Hyperplasia, lymphoid				1 (2%)
Necrosis			1 (8%)	
Spleen	(34)	(19)	(20)	(49)
Angiectasis	1 (3%)			
Cyst		1 (5%)		
Depletion lymphoid	5 (15%)	3 (16%)	6 (30%)	2 (4%)
Necrosis			1 (5%)	
Red pulp, hematopoietic cell proliferation, diffuse	5 (15%)	8 (42%)	7 (35%)	7 (14%)
Thymus	(21)	(5)	(11)	(27)
Necrosis, acute				1 (4%)
INTEGUMENTARY SYSTEM				
Skin	(34)	(32)	(26)	(49)
Acanthosis	3 (9%)	3 (9%)	1 (4%)	10 (20%)
Alopecia	5 (15%)	8 (25%)	2 (8%)	12 (24%)
Cyst epithelial inclusion		1 (3%)		
Hyperkeratosis		1 (3%)		
Inflammation, acute	1 (3%)			
Inflammation, chronic active			1 (4%)	
Metaplasia, osseous, focal	1 (3%)			
Necrosis	1 (3%)			
Ulcer	2 (6%)	5 (16%)	4 (15%)	5 (10%)
Ulcer, focal			1 (4%)	
Subcutaneous tissue, fibrosis				1 (2%)
Subcutaneous tissue, inflammation, acute			2 (8%)	2 (4%)
Subcutaneous tissue, inflammation, chronic		1 (3%)		
Subcutaneous tissue, inflammation, chronic active	2 (6%)	3 (9%)	5 (19%)	2 (4%)
Subcutaneous tissue, mineralization				1 (2%)
Subcutaneous tissue, necrosis, acute			1 (4%)	
Subcutaneous tissue, lymphatic, dilatation	3 (9%)			1 (2%)
MUSCULOSKELETAL SYSTEM				
Bone	(35)	(36)	(29)	(49)
Joint, tarsal, hyperostosis	18 (51%)	26 (72%)	14 (48%)	12 (24%)
NERVOUS SYSTEM				
Brain	(35)	(12)	(16)	(49)
Cyst epithelial inclusion	1 (3%)			
Meninges, infiltration cellular, lymphocytic	1 (3%)			
RESPIRATORY SYSTEM				
Lung	(35)	(15)	(19)	(49)
Alveolar epithelium, hyperplasia	1 (3%)	1 (7%)		2 (4%)
Alveolar epithelium, hyperplasia, focal		1 (7%)		
Alveolar epithelium, bronchiole, hyperplasia				1 (2%)
Peribronchiolar, glands, inflammation, acute				1 (2%)
Perivascular, infiltration cellular, lymphocytic				2 (4%)
Nose	(35)	(13)	(16)	(49)
Glands, inflammation, acute, focal	4 (11%)	1 (8%)	3 (19%)	47 (96%)
Nasolacrimal duct, inflammation, acute, focal		1 (8%)		2 (4%)
Olfactory epithelium, atrophy			1 (6%)	
Olfactory epithelium, metaplasia, focal	2 (6%)	1 (8%)	2 (13%)	46 (94%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
SPECIAL SENSES SYSTEM				
Eye		(1)		(1)
Cornea, hyperplasia, focal		1 (100%)		
Lens, cataract				1 (100%)
Harderian gland	(27)	(12)	(13)	(35)
Inflammation, chronic active				1 (3%)
URINARY SYSTEM				
Kidney	(35)	(14)	(20)	(49)
Cyst				4 (8%)
Hydronephrosis	1 (3%)	1 (7%)	1 (5%)	
Infarct	1 (3%)			
Inflammation, acute		2 (14%)	1 (5%)	
Inflammation, chronic active	3 (9%)		2 (10%)	
Nephropathy, chronic	1 (3%)			1 (2%)
Capsule, fibrosis	1 (3%)			
Pelvis, inflammation, acute			1 (5%)	
Renal tubule, dilatation	3 (9%)		2 (10%)	1 (2%)
Renal tubule, dilatation, diffuse			1 (5%)	
Renal tubule, metaplasia, osseous			1 (5%)	
Renal tubule, mineralization			1 (5%)	
Renal tubule, regeneration	12 (34%)			17 (35%)
Urethra	(3)	(2)	(4)	
Calculus micro observation only	2 (67%)	1 (50%)	2 (50%)	
Inflammation, acute		1 (50%)	3 (75%)	
Inflammation, chronic active	1 (33%)			
Urinary bladder	(33)	(11)	(15)	(49)
Calculus micro observation only	1 (3%)			
Dilatation	5 (15%)	3 (27%)	8 (53%)	3 (6%)
Inflammation, acute		1 (9%)		
Inflammation, chronic active	1 (3%)		1 (7%)	
Mucosa, hyperplasia	1 (3%)	1 (9%)	1 (7%)	

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Untreated Control	Low Dose	Mid Dose	High Dose
Animals initially in study	35	50	50	50
Animals removed	35	50	50	50
Animals examined histopathologically	35	50	50	49
ALIMENTARY SYSTEM				
Intestine large, cecum	(34)	*(50)	*(50)	(45)
Leiomyoma	1 (3%)			
Intestine large, colon	(34)	*(50)	*(50)	(47)
Leiomyoma		1 (2%)		
Intestine small, jejunum	(34)	*(50)	*(50)	(47)
Peyer's patch, lymphoma malignant histiocytic	1 (3%)			
Peyer's patch, lymphoma malignant lymphocytic	4 (12%)			
Peyer's patch, lymphoma malignant mixed	1 (3%)			1 (2%)
Liver	(34)	(50)	(49)	(48)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangioma				1 (2%)
Hemangiosarcoma				4 (8%)
Hemangiosarcoma, multiple		1 (2%)	1 (2%)	4 (8%)
Hemangiosarcoma, metastatic, spleen			2 (4%)	
Hepatocellular carcinoma		1 (2%)		2 (4%)
Hepatocellular adenoma	1 (3%)	3 (6%)	5 (10%)	9 (19%)
Hepatocellular adenoma, multiple			1 (2%)	21 (44%)
Lymphoma malignant histiocytic	1 (3%)	1 (2%)	2 (4%)	1 (2%)
Lymphoma malignant lymphocytic		3 (6%)	2 (4%)	1 (2%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant mixed		6 (12%)	1 (2%)	
Lymphoma malignant undifferentiated cell type		1 (2%)		
Mesentery	*(35)	*(50)	*(50)	*(49)
Hemangiosarcoma				1 (2%)
Lymphoma malignant mixed		1 (2%)		
Myxosarcoma, metastatic, skin				1 (2%)
Pancreas	(34)	*(50)	*(50)	(46)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Lymphoma malignant lymphocytic	1 (3%)	1 (2%)		1 (2%)
Lymphoma malignant mixed		2 (4%)		
Salivary glands	(35)	*(50)	*(50)	(46)
Lymphoma malignant lymphocytic	3 (9%)			2 (4%)
Lymphoma malignant mixed				1 (2%)
Stomach, forestomach	(33)	*(50)	*(50)	(47)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic				1 (2%)
Papilloma squamous	1 (3%)			
Tongue	*(35)	*(50)	*(50)	*(49)
Mucosa, dorsal, squamous cell carcinoma			1 (2%)	
CARDIOVASCULAR SYSTEM				
Heart	(35)	*(50)	*(50)	(48)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Lymphoma malignant		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland	(35)	(50)	(47)	(49)
Capsule, adenoma		2 (4%)		
Capsule, carcinoma		1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM (Continued)				
Adrenal gland, cortex	(35)	(49)	(47)	(49)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)		
Lymphoma malignant mixed		1 (2%)		
Adrenal gland, medulla	(35)	(49)	(46)	(49)
Pheochromocytoma malignant		1 (2%)		1 (2%)
Pheochromocytoma benign		1 (2%)	2 (4%)	9 (18%)
Bilateral, pheochromocytoma benign				29 (59%)
Islets, pancreatic	(34)	*(50)	*(50)	(46)
Carcinoma		2 (4%)		
Pituitary gland	(32)	*(50)	*(50)	(44)
Pars distalis, adenoma	9 (28%)	3 (6%)	4 (8%)	6 (14%)
Pars distalis, adenoma, multiple	1 (3%)			
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(34)	*(50)	*(50)	(46)
Follicular cell, adenoma	3 (9%)			3 (7%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(34)	*(50)	*(50)	(48)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant mixed		2 (4%)		
Periovarian tissue, lymphoma malignant histiocytic				1 (2%)
Periovarian tissue, lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Periovarian tissue, lymphoma malignant		1 (2%)		
Periovarian tissue, lymphoma malignant mixed	1 (3%)	1 (2%)	1 (2%)	2 (4%)
Uterus	(34)	*(50)	*(50)	(47)
Leiomyoma			1 (2%)	1 (2%)
Leiomyosarcoma				1 (2%)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)		
Lymphoma malignant mixed		1 (2%)		
HEMATOPOIETIC SYSTEM				
Bone marrow	(35)	*(50)	*(50)	(48)
Hemangiosarcoma				1 (2%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic		1 (2%)		
Lymph node	(34)	*(50)	*(50)	(44)
Lymphoma malignant lymphocytic	1 (3%)			1 (2%)
Lymphoma malignant		1 (2%)		
Axillary, lymphoma malignant histiocytic		1 (2%)		
Deep cervical, lymphoma malignant histiocytic				1 (2%)
Deep cervical, lymphoma malignant mixed		1 (2%)		
Inguinal, lymphoma malignant lymphocytic		1 (2%)		
Inguinal, lymphoma malignant		1 (2%)		
Inguinal, lymphoma malignant mixed		2 (4%)		
Lumbar, lymphoma malignant histiocytic	1 (3%)	1 (2%)		
Lumbar, lymphoma malignant lymphocytic		1 (2%)	1 (2%)	1 (2%)
Lumbar, lymphoma malignant mixed			1 (2%)	
Mediastinal, lymphoma malignant histiocytic	1 (3%)			2 (5%)
Mediastinal, lymphoma malignant lymphocytic		1 (2%)		2 (5%)
Mediastinal, lymphoma malignant mixed	1 (3%)	4 (8%)		1 (2%)
Mesenteric, lymphoma malignant histiocytic	1 (3%)	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM				
Lymph node (Continued)	(34)	*(50)	*(50)	(44)
Mesenteric, lymphoma malignant lymphocytic		1 (2%)		5 (11%)
Mesenteric, lymphoma malignant mixed	2 (6%)	7 (14%)	3 (6%)	1 (2%)
Pancreatic, lymphoma malignant histiocytic		1 (2%)		1 (2%)
Pancreatic, lymphoma malignant lymphocytic				2 (5%)
Renal, lymphoma malignant histiocytic	1 (3%)	1 (2%)	1 (2%)	
Renal, lymphoma malignant lymphocytic		1 (2%)		
Renal, lymphoma malignant mixed	1 (3%)	6 (12%)	1 (2%)	
Lymph node, mandibular	(33)	*(50)	*(50)	(42)
Lymphoma malignant histiocytic	1 (3%)	1 (2%)		2 (5%)
Lymphoma malignant lymphocytic	8 (24%)	1 (2%)		9 (21%)
Lymphoma malignant mixed	2 (6%)	3 (6%)	1 (2%)	3 (7%)
Spleen	(34)	*(50)	*(50)	(47)
Hemangiosarcoma			2 (4%)	2 (4%)
Lymphoma malignant histiocytic	1 (3%)	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	10 (29%)	3 (6%)	2 (4%)	10 (21%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant mixed	2 (6%)	7 (14%)	3 (6%)	3 (6%)
Lymphoma malignant undifferentiated cell type		1 (2%)	1 (2%)	
Thymus	(30)	*(50)	*(50)	(43)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant lymphocytic				2 (5%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant mixed	1 (3%)	1 (2%)		3 (7%)
Thymoma malignant	1 (3%)			
INTEGUMENTARY SYSTEM				
Mammary gland	(33)	*(50)	*(50)	(40)
Adenocarcinoma	3 (9%)	1 (2%)	2 (4%)	4 (10%)
Skin	(35)	*(50)	*(50)	(46)
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, myxosarcoma				1 (2%)
Subcutaneous tissue, sarcoma		1 (2%)		
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(35)	*(50)	*(50)	*(49)
Sarcoma, metastatic, skin		1 (2%)		
NERVOUS SYSTEM				
None				
RESPIRATORY SYSTEM				
Lung	(35)	*(50)	*(50)	(48)
Adenocarcinoma, metastatic, mammary gland	1 (3%)			1 (2%)
Alveolar/bronchiolar adenoma	1 (3%)	2 (4%)	1 (2%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma				1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (3%)			
Hepatocellular carcinoma, metastatic				1 (2%)
Lymphoma malignant histiocytic	1 (3%)		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic		1 (2%)		5 (10%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant mixed		1 (2%)		1 (2%)
Lymphoma malignant undifferentiated cell type		1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
RESPIRATORY SYSTEM				
Lung (Continued)	(35)	*(50)	*(50)	(48)
Mediastinum, lymphoma malignant lymphocytic	1 (3%)			
Mediastinum, lymphoma malignant mixed			1 (2%)	1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland	*(35)	*(50)	*(50)	*(49)
Adenoma	2 (6%)	1 (2%)	1 (2%)	3 (6%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant		1 (2%)		
URINARY SYSTEM				
Kidney	(34)	*(50)	*(50)	(48)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	8 (24%)	2 (4%)		4 (8%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant mixed	1 (3%)	2 (4%)	3 (6%)	1 (2%)
Urinary bladder	(34)	*(50)	*(50)	(47)
Lymphoma malignant lymphocytic				4 (9%)
Lymphoma malignant mixed	1 (3%)			
SYSTEMIC LESIONS				
Multiple organs	*(35)	*(50)	*(50)	*(49)
Lymphoma malignant lymphocytic	11 (31%)	4 (8%)	4 (8%)	11 (22%)
Lymphoma malignant mixed	3 (9%)	11 (22%)	6 (12%)	3 (6%)
Lymphoma malignant histiocytic	1 (3%)	1 (2%)	3 (6%)	2 (4%)
Lymphoma malignant		1 (2%)		
Lymphoma malignant undifferentiated cell		1 (2%)	1 (2%)	
Hemangiosarcoma		1 (2%)	3 (6%)	8 (16%)
Hemangioma				1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	35	50	50	50
Terminal sacrifice	29	28	38	39
Natural death	3	15	10	11
Moribund sacrifice	3	6	2	
Drowned		1		
TUMOR SUMMARY				
Total animals with primary neoplasms **	24	29	25	46
Total primary neoplasms	39	42	36	118
Total animals with benign neoplasms	13	12	13	44
Total benign neoplasms	19	15	15	84
Total animals with malignant neoplasms	18	24	18	31
Total malignant neoplasms	20	27	21	34
Total animals with secondary neoplasms ***	1	1	3	4
Total secondary neoplasms	1	1	4	4

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: UNTREATED CONTROL

WEEKS ON STUDY	071	092	098	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105
CARCASS ID	405	383	364	411	413	362	361	391	392	403	421	422	424	363	365	374	382	384	385	393	395	402	412	423	372
ALIMENTARY SYSTEM																									
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma								X																	
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant histiocytic					X																				
Peyer's patch, lymphoma malignant lymphocytic									X															X	
Peyer's patch, lymphoma malignant mixed																			X						
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Lymphoma malignant histiocytic					X																				
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X		X					X				
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous										X															
Stomach, glandular	+	A	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X		X	X					X				X			X		
Pars distalis, adenoma, multiple					X																				
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X				X					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perivarian tissue, lymphoma malignant mixed																			X						
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A. Autolysis precludes examination
X Incidence of listed morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	373	375	425	371	381	394	401	404	414	415	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	34
Gallbladder	+	+	+	+	+	+	+	+	+	+	32
Intestine large	+	+	+	+	+	+	+	+	+	+	34
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	34
Leiomyoma											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	34
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	34
Intestine small	+	+	+	+	+	+	+	+	+	+	34
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	34
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	34
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	34
Peyer's patch, lymphoma malignant histiocytic											1
Peyer's patch, lymphoma malignant lymphocytic	X					X					4
Peyer's patch, lymphoma malignant mixed											1
Liver	+	+	+	+	+	+	+	+	+	+	34
Hepatocellular adenoma			X								1
Lymphoma malignant histiocytic											1
Pancreas	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant lymphocytic					X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	35
Lymphoma malignant lymphocytic											3
Stomach	+	+	+	+	+	+	+	+	+	+	34
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	33
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	33
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	35
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	35
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	35
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	35
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	34
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	I	32
Pars distalis, adenoma			X					X			9
Pars distalis, adenoma, multiple											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	34
Follicular cell, adenoma									X		3
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Ovary	+	+	+	+	+	+	+	+	+	+	34
Perlovarian tissue, lymphoma malignant mixed											1
Uterus	+	+	+	+	+	+	+	+	+	+	34

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	071	092	098	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105
CARCASS ID	405	383	364	411	413	362	361	391	392	403	421	422	424	363	365	374	382	384	385	393	395	402	412	423	372
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X																						
Lumbar, lymphoma malignant histiocytic					X																				
Mediastinal, lymphoma malignant histiocytic					X																				
Mediastinal, lymphoma malignant mixed																				X					
Mesenteric, lymphoma malignant histiocytic					X																				
Mesenteric, lymphoma malignant mixed																			X	X					
Renal, lymphoma malignant histiocytic					X																				
Renal, lymphoma malignant mixed																				X					
Lymph node, mandibular	+	A		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic									X					X		X					X				
Lymphoma malignant mixed																			X						
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic					X																				
Lymphoma malignant lymphocytic			X						X			X		X		X					X			X	
Lymphoma malignant mixed																			X						
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+		+
Lymphoma malignant mixed																			X						
Thymoma malignant																				X					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma, multiple																									
Lymphoma malignant histiocytic					X																				
Mediastinum, lymphoma malignant lymphocytic			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma								X																	
URINARY SYSTEM																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X									X		X		X					X				
Lymphoma malignant mixed																			X						
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																				X					

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	3733	3755	4245	3771	3881	3994	4001	4044	4144	4115	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	35
Lymph node	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant lymphocytic											1
Lumbar, lymphoma malign histiocytic											1
Mediastinal, lymphoma malignant histiocytic											1
Mediastinal, lymphoma malign mixed											1
Mesenteric, lymphoma malignant histiocytic											1
Mesenteric, lymphoma malignant mixed											2
Renal, lymphoma malignant histiocytic											1
Renal, lymphoma malignant mixed											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	33
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic	X			X	X	X					8
Lymphoma malignant mixed							X				2
Spleen	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant histiocytic											1
Lymphoma malignant lymphocytic				X	X	X					10
Lymphoma malignant mixed							X				2
Thymus	+	+	+	+	+	+	+	+	+	+	30
Lymphoma malignant mixed											1
Thymoma malignant											1
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	33
Adenocarcinoma					X			X			3
Skin	+	+	+	+	+	+	+	+	+	+	35
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	35
Skeletal muscle											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	35
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	35
Adenocarcinoma, metastatic, mammary gland								X			1
Alveolar/bronchiolar adenoma											1
Alveolar/bronchiolar carcinoma, multiple									X		1
Lymphoma malignant histiocytic											1
Mediastinum, lymphoma malignant lymphocytic											1
Nose	+	+	+	+	+	+	+	+	+	+	35
Trachea	+	+	+	+	+	+	+	+	+	+	34
SPECIAL SENSES SYSTEM											
Harderian gland	+	+	+	+	M	M	M	+	+	+	29
Adenoma										X	2
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant lymphocytic				X	X	X					8
Lymphoma malignant mixed											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	34
Lymphoma malignant mixed											1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: LOW DOSE

WEEKS ON STUDY	046	064	065	069	071	075	078	081	081	082	086	090	091	091	092	093	096	101	102	102	102	103	104	104	104
CARCASS ID	971	963	931	965	984	951	991	021	953	985	955	954	993	005	975	004	002	935	111	001	003	024	941	943	952
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Gallbladder	+	+	A	+	+	+	+	+	+	A	+	A	+	+											
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+											
Intestine large, cecum	+	+	A	A	+	+	+	+	+	+	+	A		+											
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+		+											
Leiomyoma																									
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	M	+		+											
Intestine small	+	+	A	A	+	+	+	+	+	+	+	+	+	+											
Intestine small, duodenum	+	+	A	A	+	A	+	+	+	+	+	+		+											
Intestine small, ileum	+	+	A	A	+	+	+	+	+	+	+	A		+											
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	+	+	A		+											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																									
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic				X							X														
Lymphoma malignant			X																						
Lymphoma malignant mixed								X												X	X		X		X
Lymphoma malignant undifferentiated cell type							X																		
Mesentery									+			+		+							+				
Lymphoma malignant mixed																					X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+				
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed								X													X				
Salivary glands	+	+	M	+	+	+	+	M	+	+	+	+	+	+											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+											
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Lymphoma malignant			X																						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Capsule, carcinoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant mixed																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Carcinoma																									
Parathyroid gland	+	M	M	+	M	+	+	+	+	+	+	+	+	+											
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+											
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	+	+		
Lymphoma malignant mixed								X															X		
Perovarian tissue, lymphoma malignant lymphocytic				X																					
Perovarian tissue, lymphoma malignant			X																						
Perovarian tissue, lymphoma malignant mixed																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+				+	+	
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant mixed								X																	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	9962	9964	9972	9974	0012	0015	9932	9934	9944	9995	9933	9973	0022	0023	0025	9942	9945	9961	9981	9982	9983	9992	9994	0013	0014	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										14
Gallbladder																										11
Intestine large										+																14
Intestine large, cecum																										10
Intestine large, colon										+																13
Leiomyoma										X																1
Intestine large, rectum																										11
Intestine small																										12
Intestine small, duodenum																										10
Intestine small, ileum																										10
Intestine small, jejunum																										10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple					X																					1
Hepatocellular carcinoma																										1
Hepatocellular adenoma		X			X						X															3
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic					X																					3
Lymphoma malignant																										1
Lymphoma malignant mixed																						X				6
Lymphoma malignant undifferentiated cell type																										1
Mesentery																										4
Lymphoma malignant mixed																										1
Pancreas																				+						16
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										2
Salivary glands																										12
Stomach																										14
Stomach, forestomach																										14
Stomach, glandular																										13
CARDIOVASCULAR SYSTEM																										
Heart																										14
Lymphoma malignant																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																		X				X				2
Capsule, carcinoma																				X						1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																						X				1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																						X				1
Pheochromocytoma benign																										1
Islets, pancreatic																	+		+							16
Carcinoma																	X		X							2
Parathyroid gland																										11
Pituitary gland		+								+	+								+							17
Pars distalis, adenoma		X								X	X															3
Pars intermedia, adenoma																			X							1
Thyroid gland																										14
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary				+												+			+						+	24
Lymphoma malignant mixed																										2
Periovarian tissue, lymphoma malignant lymphocytic																										1
Periovarian tissue, lymphoma malignant																										1
Periovarian tissue, lymphoma malignant mixed																										1
Uterus	+			+	+	+		+	+			+	+	+	+	+	+	+		+				+	+	36
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	046	064	065	069	071	075	078	081	081	082	086	090	091	091	092	093	096	101	102	102	102	103	104	104	104
CARCASS ID	971	963	931	965	984	951	991	021	533	985	955	954	993	005	975	004	002	935	111	001	003	024	041	943	952
HEMATOPOIETIC SYSTEM																									
Blood				+																					
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+											
Lymphoma malignant lymphocytic											X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+	+	+		+		
Lymphoma malignant			X																						
Axillary, lymphoma malignant histiocytic																X									
Deep cervical, lymphoma malignant mixed																				X					
Inguinal, lymphoma malignant lymphocytic				X																					
Inguinal, lymphoma malignant			X																						
Inguinal, lymphoma malignant mixed								X												X					
Lumbar, lymphoma malignant histiocytic																X									
Lumbar, lymphoma malignant lymphocytic				X																					
Mediastinal, lymphoma malignant lymphocytic				X																					
Mediastinal, lymphoma malignant mixed																				X	X		X		
Mesenteric, lymphoma malignant histiocytic																X									
Mesenteric, lymphoma malignant lymphocytic				X																					
Mesenteric, lymphoma malignant mixed																			X	X	X		X		
Pancreatic, lymphoma malignant histiocytic																X									
Renal, lymphoma malignant histiocytic																X									
Renal, lymphoma malignant lymphocytic				X																					
Renal, lymphoma malignant mixed								X											X	X	X				
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	+	+	+		+				+			+		
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant mixed																				X			X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+
Lymphoma malignant histiocytic																X									
Lymphoma malignant lymphocytic				X							X														
Lymphoma malignant			X																						
Lymphoma malignant mixed								X											X	X			X		X
Lymphoma malignant undifferentiated cell type							X																		
Thymus	+	M	+	+	M	+	M	+	M	+	M	M	+	+		+									
Lymphoma malignant histiocytic																X									
Lymphoma malignant			X																						
Lymphoma malignant mixed								X																	
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	M	+	M	M	M	+	+	M	M	M	+	+										
Adenocarcinoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+										+	+
Subcutaneous tissue, fibrosarcoma																									X
Subcutaneous tissue, sarcoma		X																							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Skeletal muscle		+																							
Sarcoma, metastatic, skin		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Alveolar/bronchiolar adenoma			X																						
Alveolar/bronchiolar adenoma, multiple									X																
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant			X																						
Lymphoma malignant mixed								X																	
Lymphoma malignant undifferentiated cell type							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
SPECIAL SENSES SYSTEM																									
Eye							+																		
Harderian gland	+	+	+	+	+	+	M	+	+	+	M	+	M	+											
Adenoma																									
Lymphoma malignant			X																						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Lymphoma malignant lymphocytic				X							X														
Lymphoma malignant			X																						
Lymphoma malignant mixed								X																	
Urethra	+																								
Urinary bladder	+	+	A	+	+	+	M	+	+	+	+	+	+	+											

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	9962	9964	9972	9974	0012	0015	9932	9934	9944	9995	9933	9973	0022	0023	0025	9942	9945	9961	9981	9982	9983	9992	9994	0113	0114	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow																										13
Lymphoma malignant lymphocytic																										1
Lymph node									+				+					+				+				23
Lymphoma malignant																										1
Axillary, lymphoma malignant histiocytic																										1
Deep cervical, lymphoma malignant mixed																										1
Inguinal, lymphoma malignant lymphocytic																										1
Inguinal, lymphoma malignant																										1
Inguinal, lymphoma malignant mixed																										2
Lumbar, lymphoma malign histiocytic																										1
Lumbar, lymphoma malign lymphocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malign mixed																						X				4
Mesenteric, lymphoma malignant histiocytic																										1
Mesenteric, lymphoma malignant lymphocytic																										1
Mesenteric, lymphoma malignant mixed									X				X									X				7
Pancreatic, lymphoma malignant histiocytic																										1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malign lymphocytic																										1
Renal, lymphoma malignant mixed																		X				X				6
Lymph node, mandibular																						+				16
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																						X				3
Spleen											+											+	+			26
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic											X															3
Lymphoma malignant																										1
Lymphoma malignant mixed																						X	X			7
Lymphoma malignant undifferentiated cell type																										1
Thymus																										9
Lymphoma malignant histiocytic																										1
Lymphoma malignant																										1
Lymphoma malignant mixed																										1
INTEGUMENTARY SYSTEM																										
Mammary gland																										6
Adenocarcinoma																										1
Skin		+		+	+								+											+	+	22
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										14
Skeletal muscle																										1
Sarcoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain																										14
RESPIRATORY SYSTEM																										
Lung							+																			15
Alveolar/bronchiolar adenoma							X																			2
Alveolar/bronchiolar adenoma multiple																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Nose																										14
Trachea																										14
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland								+																		12
Adenoma								X																		1
Lymphoma malignant																										1
URINARY SYSTEM																										
Kidney																						+				15
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Lymphoma malignant mixed																						X				2
Urethra																										1
Urinary bladder																										12

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: MID DOSE

WEEKS ON STUDY	0 7 4	0 9 0	0 9 1	0 9 1	0 9 1	0 9 3	0 9 9	1 0 0	1 0 1	1 0 1	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	1 5 9 3	1 6 1 3	1 6 0 2	1 5 5 4	1 5 9 1	1 6 1 4	1 5 6 4	1 5 4 2	1 5 5 5	1 5 8 2	1 6 2 5	1 5 4 4	1 5 3 5	1 5 5 2	1 5 5 3	1 5 7 1	1 5 7 5	1 5 9 2	1 5 9 4	1 6 0 1	1 6 0 3	1 6 2 2	1 6 2 3	1 5 3 2	1 5 3 3
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	+																				
Gallbladder	A	+	+	A	+																				
Intestine large	+	+	+	+	+	A																			
Intestine large, cecum	A		+	+	+	A																			
Intestine large, colon	+		+	+	+	A																			
Intestine large, rectum	+		+	+	+	A																			
Intestine small	A	+	+	+	+	A																			
Intestine small, duodenum	A		+	+	+	A																			
Intestine small, ileum	A		+	+	+	A																			
Intestine small, jejunum	A		+	+	+	A																			
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Hemangiosarcoma, multiple								X																	
Hemangiosarcoma, metastatic, spleen												X													
Hepatocellular adenoma															X								X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic	X								X																
Lymphoma malignant lymphocytic																	X						X		
Lymphoma malignant mixed																									
Mesentery					+																				
Pancreas	+	+	+	+	+																				
Hemangiosarcoma, metastatic, spleen																									
Salivary glands	M	+	+	M	+																				
Stomach	+	+	+	+	+	A																			
Stomach, forestomach	+	+	+	+	+	A																			
Lymphoma malignant histiocytic	X																								
Stomach, glandular	+	+	+	+	+	A																			
Tongue																									
Mucosa, dorsal, squamous cell carcinoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+																				
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+		+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+																				
Parathyroid gland	M	+	+	M	+																				
Pituitary gland	M	+	+	+	+						A					+									
Pars distalis, adenoma																									
Thyroid gland	M	+	+	+	+																				
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+		+		+								+								
Lymphoma malignant histiocytic	X																								
Perovarian tissue, lymphoma malignant mixed																									
Uterus	+	+	+	+	+		+					+	+	+	+	+	+	+	+		+	+	+		+
Leiomyoma							X																		
Lymphoma malignant histiocytic	X																								

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	15344	15511	15744	16044	16065	16244	15433	15455	15633	15721	15733	15881	16111	16122	16211	15311	15411	15611	15622	15655	15833	15844	15855	15955	16155	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										4
Gallbladder																										3
Intestine large																										5
Intestine large, cecum																										3
Intestine large, colon																										4
Intestine large, rectum																										4
Intestine small																										4
Intestine small, duodenum																										3
Intestine small, ileum																										3
Intestine small, jejunum																										3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma, multiple																										1
Hemangiosarcoma, metastatic, spleen																					X					2
Hepatocellular adenoma									X		X										X					5
Hepatocellular adenoma, multiple																			X							1
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																			X							1
Mesentery																										1
Pancreas															+						+					7
Hemangiosarcoma, metastatic, spleen																					X					1
Salivary glands																										3
Stomach																										5
Stomach, forestomach																										5
Lymphoma malignant histiocytic																										1
Stomach, glandular																										5
Tongue																					+					1
Mucosa, dorsal, squamous cell carcinoma																					X					1
CARDIOVASCULAR SYSTEM																										
Heart																										5
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pheochromocytoma benign								X											X							2
Islets, pancreatic																										5
Parathyroid gland																										3
Pituitary gland				+			I			+							+		+							9
Pars distalis, adenoma				X						X							X		X							4
Thyroid gland																										4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+			+	+			+		+	+							+				+			17
Lymphoma malignant histiocytic																										1
Periovarian tissue, lymphoma malignant mixed									X																	1
Uterus	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	41
Leiomyoma																										1
Lymphoma malignant histiocytic																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	074	090	091	091	091	093	099	100	101	101	102	102	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	15933	16133	16022	15544	15911	16144	15644	15422	15555	15822	16225	15444	15335	15522	15533	15711	15755	15922	15944	16001	16033	16222	16233	15322	15333
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+																				
Lymph node	+	+	+	M	+							+					+								
Lumbar, lymphoma malignant lymphocytic																	X								
Lumbar, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant mixed																									
Renal, lymphoma malignant histiocytic	X																								
Renal, lymphoma malignant mixed																									
Lymph node, mandibular		+	+	M	+																				
Lymphoma malignant mixed																									
Spleen	A	+	+	+	+			+	+			+			+	+				+					
Hemangiosarcoma												X													
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																X									
Lymphoma malignant mixed																				X					
Lymphoma malignant undifferentiated cell type																									
Thymus	+	+	+	+	M				+																
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+						+				+										
Adenocarcinoma											X				X										
Skin	+	+	+	+	+											+	+			+	+				
Subcutaneous tissue, fibrosarcoma																X									
Subcutaneous tissue, hemangiosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+																				
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+																				
Alveolar/bronchiolar adenoma					X																				
Lymphoma malignant histiocytic	X																								
Mediastinum, lymphoma malignant mixed																									
Nose	+	+	+	+	+																				
Trachea	M	+	+	+	+																				
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	M	M	+																				
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+																				
Lymphoma malignant mixed																									
Urinary bladder	+	+	+	+	+																				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	15334	15551	15574	16004	16005	16024	15433	15455	15663	15672	15673	15881	16111	16112	16211	15531	15541	15561	15562	15565	15583	15584	15585	15595	16115	
HEMATOPOIETIC SYSTEM																										
Bone marrow																										5
Lymph node									+			+					+		+		+					11
Lumbar, lymphoma malig lymphocytic																										1
Lumbar, lymphoma malignant mixed									X																	1
Mesenteric, lymphoma malignant mixed									X			X							X							3
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malignant mixed									X																	1
Lymph node, mandibular																			+							4
Lymphoma malignant mixed																			X							1
Spleen				+					+			+		+		+					+		+			17
Hemangiosarcoma																					X					2
Lymphoma malignant histiocytic														X												1
Lymphoma malignant lymphocytic									X																	2
Lymphoma malignant mixed												X											X			3
Lymphoma malignant undifferentiated cell type																X										1
Thymus																										5
INTEGUMENTARY SYSTEM																										
Mammary gland																										7
Adenocarcinoma																										2
Skin					+		+						+	+			+		+	+	+				+	18
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																					X					1
MUSCULOSKELETAL SYSTEM																										
Bone																										5
NERVOUS SYSTEM																										
Brain																										5
RESPIRATORY SYSTEM																										
Lung												+														6
Alveolar/bronchiolar adenoma																										1
Lymphoma malignant histiocytic																										1
Mediastinum, lymphoma malign mixed												X														1
Nose																										5
Trachea																										4
SPECIAL SENSES SYSTEM																										
Harderian gland													+													4
Adenoma													X													1
URINARY SYSTEM																										
Kidney									+		+	+														8
Lymphoma malignant mixed									X		X	X														3
Urinary bladder																										5

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7: HIGH DOSE

WEEKS ON STUDY	0 7 0	0 7 2	0 7 4	0 7 6	0 8 0	0 8 8	0 9 4	0 9 6	0 9 6	0 9 9	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	2 2 2 5	2 1 3 1	2 1 9 2	2 1 8 5	2 1 9 1	2 2 0 1	2 2 0 3	2 1 5 3	2 1 6 5	2 1 7 2	2 2 2 1	2 1 3 5	2 1 4 3	2 1 4 4	2 1 5 1	2 1 6 1	2 1 6 3	2 1 7 5	2 1 8 2	2 1 8 4	2 2 2 4	2 1 3 4	2 1 4 5	2 1 6 4	2 1 7 4
ALIMENTARY SYSTEM																									
Esophagus		+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder		A	A	+	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum		A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum		A	A	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum		A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum		A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant mixed																X									
Liver		+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X											
Hemangiosarcoma										X										X					
Hemangiosarcoma, multiple						X					X												X		
Hepatocellular carcinoma																									
Hepatocellular adenoma								X							X										
Hepatocellular adenoma, multiple												X	X	X					X	X	X		X		X
Lymphoma malignant histiocytic							X																		
Lymphoma malignant lymphocytic																								X	
Mesentery																									
Hemangiosarcoma																									
Myxosarcoma, metastatic, skin																									
Pancreas		A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Salivary glands		+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																X									
Stomach		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach, glandular		+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen											X														
ENDOCRINE SYSTEM																									
Adrenal gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign									X	X		X				X						X	X		
Bilateral, pheochromocytoma benign					X	X					X		X	X	X			X	X	X	X			X	X
Islets, pancreatic		A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland		M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland		M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Pars distalis, adenoma														X								X			
Thyroid gland		+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X																
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary		+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periovarian tissue, lymphoma malignant histiocytic																									
Periovarian tissue, lymphoma malignant lymphocytic																					X				
Periovarian tissue, lymphoma malignant mixed																X									
Uterus		+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																X									
Leiomyosarcoma																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	21193	21194	21195	22005	22222	22323	21132	21332	21522	21544	21555	21626	21711	21731	21811	22022	22044	22111	21411	21422	21183	22212	22213	22214	22215	
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Peyer's patch, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																										1
Hemangiosarcoma		X																	X							4
Hemangiosarcoma, multiple																					X					4
Hepatocellular carcinoma												X									X					2
Hepatocellular adenoma		X		X	X	X			X									X						X		9
Hepatocellular adenoma, multiple	X									X	X	X	X	X		X			X	X	X		X		X	X	21
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Mesentery								+													+					2
Hemangiosarcoma																					X					1
Myxosarcoma, metastatic, skin								X																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic						X						X														2
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma, metastatic, spleen																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																			X							1
Pheochromocytoma benign			X												X				X							9
Bilateral, pheochromocytoma benign	X	X			X	X				X	X	X	X	X		X	X				X	X	X	X	X	X	29
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Pars distalis, adenoma			X					X				X							X							6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Follicular cell, adenoma													X	X												3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Perıovarian tissue, lymphoma malignant histiocytic				X																						1
Perıovarian tissue, lymphoma malignant lymphocytic																										1
Perıovarian tissue, lymphoma malignant mixed											X															2
Uterus	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma																										1
Leiomyosarcoma																							X			1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	070	072	074	076	080	088	094	096	096	099	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	225	211	312	192	185	191	201	203	153	165	172	221	135	143	144	151	161	163	175	182	184	224	234	145	164	174
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X															
Lymphoma malignant histiocytic						X																				
Lymph node	M	+	M	A	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic								X																		
Deep cervical, lymphoma malignant histiocytic						X																				
Lumbar, lymphoma malignant lymphocytic																										
Mediastinal, lymphoma malignant histiocytic						X																				
Mediastinal, lymphoma malignant lymphocytic																										
Mediastinal, lymphoma malignant mixed																										
Mesenteric, lymphoma malignant lymphocytic												X	X									X				
Mesenteric, lymphoma malignant mixed																										
Pancreatic, lymphoma malignant histiocytic							X																			
Pancreatic, lymphoma malignant lymphocytic																									X	
Lymph node, mandibular	M	M	M	A	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																				
Lymphoma malignant lymphocytic								X				X	X	X											X	
Lymphoma malignant mixed																X										
Spleen	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X					X																
Lymphoma malignant histiocytic						X																				
Lymphoma malignant lymphocytic												X	X	X								X			X	
Lymphoma malignant mixed																X										
Thymus	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X				
Lymphoma malignant mixed																X										
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma			X				X					X														
Skin	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, myxosarcoma																										
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																										
Lung	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland			X																							
Alveolar/bronchiolar adenoma											X															
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic																										
Lymphoma malignant histiocytic							X																			
Lymphoma malignant lymphocytic												X	X													
Lymphoma malignant mixed																X										
Mediastinum, lymphoma malignant mixed																										
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Harderian gland	A	M	+	+	+	+	+	M	+	+	M	M	+	+	M	M	+	M	M	+	+	+	M	+		
Adenoma																										
Lymphoma malignant lymphocytic													X													
URINARY SYSTEM																										
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic							X																			
Lymphoma malignant lymphocytic												X													X	
Lymphoma malignant mixed																X										
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													X	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	21193	21194	21195	22005	22022	22023	21132	21333	21523	21154	21555	21622	21711	21733	21811	22020	22204	22111	21141	21142	21183	22212	22213	22214	22215	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant lymphocytic																										1
Deep cervical, lymphoma malignant histiocytic																										1
Lumbar, lymphoma malign. lymphocytic																									X	1
Mediastinal, lymphoma malignant histiocytic				X																						2
Mediastinal, lymphoma malignant lymphocytic																		X							X	2
Mediastinal, lymphoma malign mixed											X															1
Mesenteric, lymphoma malignant lymphocytic						X							X													5
Mesenteric, lymphoma malignant mixed											X															1
Pancreatic, lymphoma malignant histiocytic																										1
Pancreatic, lymphoma malignant lymphocytic						X																				2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymphoma malignant histiocytic				X																						2
Lymphoma malignant lymphocytic						X							X												X	X	9
Lymphoma malignant mixed											X				X											3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										2
Lymphoma malignant histiocytic				X																						2
Lymphoma malignant lymphocytic						X							X					X							X	X	10
Lymphoma malignant mixed											X				X											3
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant lymphocytic																		X								2
Lymphoma malignant mixed											X				X											3
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	M	+	+	M	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	40
Adenocarcinoma										X																4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Subcutaneous tissue, myxosarcoma								X																		1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, mammary gland							X																			1
Alveolar/bronchiolar adenoma									X																	2
Alveolar/bronchiolar carcinoma												X														1
Hepatocellular carcinoma, metastatic																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																		X							X	X	5
Lymphoma malignant mixed																										1
Mediastinum, lymphoma malign. mixed											X															1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SPECIAL SENSES SYSTEM																										
Harderian gland	M	+	M	+	M	M	+	+	+	+	M	M	M	M	+	M	M	M	M	M	M	M	+	M	+	23
Adenoma							X	X																	X	3
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic						X																			X	4
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic						X																			X	4

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Control	100 ppm	200 ppm	600 ppm
Adrenal Gland/Capsule: Adenoma or Carcinoma				
Overall Rates (a)	0/35 (0%)	3/50 (6%)	0/47 (0%)	0/49 (0%)
Adjusted Rates (b)	0.0%	10.7%	0.0%	0.0%
Terminal Rates (c)	0/29 (0%)	3/28 (11%)	0/38 (0%)	0/39 (0%)
Day of First Observation		727		
Life Table Tests (d)	P=0.261N	P=0.114	(e)	(e)
Logistic Regression Tests (d)	P=0.261N	P=0.114	(e)	(e)
Cochran-Armitage Trend Test (d)	P=0.282N			
Fisher Exact Test (d)		P=0.198	(e)	(e)
Adrenal Gland/Medulla: Pheochromocytoma				
Overall Rates (a)	0/35 (0%)	1/49 (2%)	2/46 (4%)	38/49 (78%)
Adjusted Rates (b)	0.0%	3.6%	5.3%	86.3%
Terminal Rates (c)	0/29 (0%)	1/28 (4%)	2/38 (5%)	33/39 (85%)
Day of First Observation		727	727	555
Life Table Tests (d)	P<0.001	P=0.493	P=0.299	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.493	P=0.299	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.583	P=0.319	P<0.001
Adrenal Gland/Medulla: Pheochromocytoma or Malignant Pheochromocytoma				
Overall Rates (a)	0/35 (0%)	2/49 (4%)	2/46 (4%)	38/49 (78%)
Adjusted Rates (b)	0.0%	7.1%	5.3%	86.3%
Terminal Rates (c)	0/29 (0%)	2/28 (7%)	2/38 (5%)	33/39 (85%)
Day of First Observation		727	727	555
Life Table Tests (d)	P<0.001	P=0.230	P=0.299	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.230	P=0.299	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.337	P=0.319	P<0.001
Harderian Gland: Adenoma				
Overall Rates (a)	2/35 (6%)	1/50 (2%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	6.9%	3.6%	2.6%	7.7%
Terminal Rates (c)	2/29 (7%)	1/28 (4%)	1/38 (3%)	3/39 (8%)
Day of First Observation	727	727	727	727
Life Table Tests (d)	P=0.412	P=0.512N	P=0.406N	P=0.634
Logistic Regression Tests (d)	P=0.412	P=0.512N	P=0.406N	P=0.634
Cochran-Armitage Trend Test (d)	P=0.360			
Fisher Exact Test (d)		P=0.367N	P=0.367N	P=0.657
Liver: Hepatocellular Adenoma				
Overall Rates (a)	1/34 (3%)	3/50 (6%)	6/49 (12%)	30/48 (63%)
Adjusted Rates (b)	3.4%	10.7%	15.8%	75.0%
Terminal Rates (c)	1/29 (3%)	3/28 (11%)	6/38 (16%)	29/39 (74%)
Day of First Observation	727	727	727	668
Life Table Tests (d)	P<0.001	P=0.291	P=0.110	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.291	P=0.110	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.465	P=0.135	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	1/34 (3%)	4/50 (8%)	6/49 (12%)	31/48 (65%)
Adjusted Rates (b)	3.4%	13.8%	15.8%	77.5%
Terminal Rates (c)	1/29 (3%)	3/28 (11%)	6/38 (16%)	30/39 (77%)
Day of First Observation	727	720	727	668
Life Table Tests (d)	P<0.001	P=0.168	P=0.110	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.172	P=0.110	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.322	P=0.135	P<0.001

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Control	100 ppm	200 ppm	600 ppm
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	1/35 (3%)	(f) 3/15 (20%)	(f) 1/6 (17%)	2/48 (4%)
Adjusted Rates (b)	3.4%			5.0%
Terminal Rates (c)	1/29 (3%)			1/39 (3%)
Day of First Observation	727			712
Life Table Test (d)				P=0.594
Logistic Regression Test (d)				P=0.593
Fisher Exact Test (d)				P=0.618
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	2/35 (6%)	(f) 3/15 (20%)	(f) 1/6 (17%)	3/48 (6%)
Adjusted Rates (b)	6.9%			7.5%
Terminal Rates (c)	2/29 (7%)			2/39 (5%)
Day of First Observation	727			712
Life Table Test (d)				P=0.626
Logistic Regression Test (d)				P=0.615
Fisher Exact Test (d)				P=0.648
Mammary Gland: Adenocarcinoma				
Overall Rates (a)	3/35 (9%)	1/50 (2%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	10.3%	2.8%	5.1%	9.3%
Terminal Rates (c)	3/29 (10%)	0/28 (0%)	1/38 (3%)	2/39 (5%)
Day of First Observation	727	643	710	528
Life Table Tests (d)	P=0.388	P=0.310N	P=0.383N	P=0.648N
Logistic Regression Tests (d)	P=0.333	P=0.226N	P=0.369N	P=0.590N
Cochran-Armitage Trend Test (d)	P=0.340			
Fisher Exact Test (d)		P=0.187N	P=0.334N	P=0.622N
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	10/32 (31%)	(f) 3/17 (18%)	(f) 4/9 (44%)	6/44 (14%)
Adjusted Rates (b)	33.2%			16.2%
Terminal Rates (c)	8/28 (29%)			6/37 (16%)
Day of First Observation	720			727
Life Table Test (d)				P=0.075N
Logistic Regression Test (d)				P=0.078N
Fisher Exact Test (d)				P=0.058N
Thyroid Gland: Follicular Cell Adenoma				
Overall Rates (a)	3/34 (9%)	(f) 0/14 (0%)	(f) 0/4 (0%)	3/46 (7%)
Adjusted Rates (b)	10.3%			7.5%
Terminal Rates (c)	3/29 (10%)			2/38 (5%)
Day of First Observation	727			670
Life Table Test (d)				P=0.535N
Logistic Regression Test (d)				P=0.526N
Fisher Exact Test (d)				P=0.509N
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	0/35 (0%)	(g) 1/50 (2%)	(h) 3/50 (6%)	8/49 (16%)
Adjusted Rates (b)	0.0%	3.6%	7.3%	18.9%
Terminal Rates (c)	0/29 (0%)	1/28 (4%)	1/38 (3%)	5/39 (13%)
Day of First Observation		727	699	611
Life Table Tests (d)	P=0.002	P=0.493	P=0.173	P=0.016
Logistic Regression Tests (d)	P<0.001	P=0.493	P=0.190	P=0.016
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.588	P=0.198	P=0.010

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Control	100 ppm	200 ppm	600 ppm
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (a)	0/35 (0%)	(g) 1/50 (2%)	(h) 3/50 (6%)	9/49 (18%)
Adjusted Rates (b)	0.0%	3.6%	7.3%	21.3%
Terminal Rates (c)	0/29 (0%)	1/28 (4%)	1/38 (3%)	6/39 (15%)
Day of First Observation		727	699	611
Life Table Tests (d)	P<0.001	P=0.493	P=0.173	P=0.010
Logistic Regression Tests (d)	P<0.001	P=0.493	P=0.190	P=0.010
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.588	P=0.198	P=0.006
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	15/35 (43%)	(g) 18/50 (36%)	(h) 13/50 (26%)	16/49 (33%)
Adjusted Rates (b)	48.2%	46.7%	32.0%	38.8%
Terminal Rates (c)	13/29 (45%)	9/28 (32%)	11/38 (29%)	14/39 (36%)
Day of First Observation	685	454	514	653
Life Table Tests (d)	P=0.200N	P=0.358N	P=0.137N	P=0.292N
Logistic Regression Tests (d)	P=0.289N	P=0.381N	P=0.088N	P=0.307N
Cochran-Armitage Trend Test (d)	P=0.300N			
Fisher Exact Test (d)		P=0.339N	P=0.082N	P=0.234N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups.
(f) Incomplete sampling of tissues
(g) Seventeen spleens were examined microscopically.
(h) Twenty-six spleens were examined microscopically.

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/48	4/48	8/48
N-Phenyl-2-naphthylamine	3/50	1/50	4/50
C.I. Disperse Yellow 3	0/50	2/50	2/50
D & C Red No. 9	1/50	4/50	5/50
C.I. Solvent Yellow 14	0/50	2/50	2/50
Rotenone	3/49	1/49	4/49
L-Ascorbic acid	2/50	(b) 1/50	3/50
TOTAL	13/347 (3.7%)	15/347 (4.3%)	28/347 (8.1%)
SD (c)	3.24%	2.76%	4.38%
Range (d)			
High	4/48	4/48	8/48
Low	0/50	1/50	2/50
Overall Historical Incidence			
TOTAL	107/2,032 (5.3%)	(b) 81/2,032 (4.0%)	184/2,032 (9.1%)
SD (c)	4.34%	2.42%	4.70%
Range (d)			
High	9/49	4/48	10/49
Low	0/50	0/50	1/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) One hepatoblastoma was also observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence of Pheochromocytomas in Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/49
N-Phenyl-2-naphthylamine	0/48
C.I. Disperse Yellow 3	0/46
D & C Red No. 9	0/50
C.I. Solvent Yellow 14	0/49
Rotenone	1/49
L-Ascorbic acid	2/50
TOTAL	3/341 (0.9%)
SD (b)	1.58%
Range (c)	
High	2/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 22/1,976 (1.1%)
SD (b)	1.53%
Range (c)	
High	3/49
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals
(d) Includes one malignant pheochromocytoma

TABLE D4c. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	1/50	0/50	1/50
N-Phenyl-2-naphthylamine	0/50	0/50	0/50
C.I. Disperse Yellow 3	0/50	0/50	0/50
D & C Red No. 9	0/50	2/50	2/50
C.I. Solvent Yellow 14	0/50	1/50	1/50
Rotenone	0/49	0/49	0/49
L-Ascorbic acid	1/50	2/50	3/50
TOTAL	2/349 (0.6%)	5/349 (1.4%)	7/349 (2.0%)
SD (b)	0.98%	1.90%	2.31%
Range (c)			
High	1/50	2/50	3/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	33/2,040 (1.5%)	(d) 33/2,040 (1.6%)	(d) 66/2,040 (3.2%)
SD (b)	2.03%	2.06%	2.73%
Range (c)			
High	4/50	4/50	6/50
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes nine angiosarcomas

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Untreated Control	Low Dose	Mid Dose	High Dose
Animals initially in study	35	50	50	50
Animals removed	35	50	50	50
Animals examined histopathologically	35	50	50	49
ALIMENTARY SYSTEM				
Intestine large, cecum	(34)	(10)	(3)	(45)
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Intestine large, colon	(34)	(13)	(4)	(47)
Parasite metazoan			1 (25%)	
Intestine small, ileum	(34)	(10)	(3)	(46)
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Liver	(34)	(50)	(49)	(48)
Basophilic focus	1 (3%)		1 (2%)	
Clear cell focus	1 (3%)	2 (4%)	1 (2%)	13 (27%)
Clear cell focus, multiple			12 (24%)	13 (27%)
Cytomegaly, diffuse				1 (2%)
Degeneration, cystic			6 (12%)	1 (2%)
Hematopoietic cell proliferation, multifocal	20 (59%)	37 (74%)	35 (71%)	45 (94%)
Infarct	2 (6%)	2 (4%)		
Inflammation, chronic active, diffuse		4 (8%)	29 (59%)	47 (98%)
Inflammation, chronic active, focal			1 (2%)	
Pigmentation, multifocal		4 (8%)	32 (65%)	48 (100%)
Bile duct, cyst			1 (2%)	2 (4%)
Bile duct, cyst, multiple			1 (2%)	
Bile duct, hyperplasia, multifocal			1 (2%)	40 (83%)
Hepatocyte, cytomegaly, diffuse		37 (74%)	49 (100%)	47 (98%)
Hepatocyte, cytomegaly, focal		1 (2%)		
Hepatocyte, necrosis, acute, diffuse		21 (42%)	49 (100%)	48 (100%)
Hepatocyte, necrosis, acute, focal	2 (6%)	4 (8%)		
Mesentery		(4)	(1)	(2)
Inflammation, acute			1 (100%)	
Inflammation, chronic active		3 (75%)		
Pancreas	(34)	(16)	(7)	(46)
Hyperplasia, lymphoid		1 (6%)		
Acinus, atrophy	5 (15%)	1 (6%)		
Duct, cyst	1 (3%)	1 (6%)		
Duct, ectasia	2 (6%)		1 (14%)	
Duct, hyperplasia	1 (3%)			
Duct, inflammation, chronic	1 (3%)			
Salivary glands	(35)	(12)	(3)	(46)
Hyperplasia, lymphoid				1 (2%)
Stomach, glandular	(33)	(13)	(5)	(47)
Necrosis, acute, focal		1 (8%)		
CARDIOVASCULAR SYSTEM				
Heart	(35)	(14)	(5)	(48)
Inflammation, chronic	1 (3%)			1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland	(35)	(50)	(47)	(49)
Accessory adrenal cortical nodule		1 (2%)		
Capsule, cyst	1 (3%)		1 (2%)	
Capsule, hyperplasia	35 (100%)	49 (98%)	47 (100%)	49 (100%)
Corticomedullary junction, cyst			2 (4%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
ENDOCRINE SYSTEM (Continued)				
Adrenal gland, cortex	(35)	(49)	(47)	(49)
Cyst		1 (2%)		
Degeneration, fatty				2 (4%)
Hematopoietic cell proliferation	1 (3%)	1 (2%)		
Hyperplasia	2 (6%)	1 (2%)		
Hypertrophy	6 (17%)	2 (4%)	5 (11%)	
Hypertrophy, focal			1 (2%)	
Adrenal gland, medulla	(35)	(49)	(46)	(49)
Hyperplasia	2 (6%)	1 (2%)	5 (11%)	17 (35%)
Pituitary gland	(32)	(17)	(9)	(44)
Pars distalis, cyst	1 (3%)			
Pars distalis, hyperplasia	16 (50%)		2 (22%)	19 (43%)
Thyroid gland	(34)	(14)	(4)	(46)
Inflammation, chronic	1 (3%)			1 (2%)
Ultimobranchial cyst				1 (2%)
Follicle, cyst	2 (6%)		1 (25%)	2 (4%)
Follicular cell, hyperplasia	5 (15%)			5 (11%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(34)	(24)	(17)	(48)
Angiectasis	2 (6%)			
Hyperplasia, tubular			1 (6%)	
Inflammation, chronic active	3 (9%)	8 (33%)	4 (24%)	
Follicle, cyst	11 (32%)	7 (29%)	10 (59%)	12 (25%)
Periovarian tissue, cyst	3 (9%)	3 (13%)	5 (29%)	3 (6%)
Uterus	(34)	(36)	(41)	(47)
Angiectasis		1 (3%)		
Inflammation, acute		4 (11%)	4 (10%)	
Inflammation, chronic active		1 (3%)		1 (2%)
Thrombus	2 (6%)			
Endometrium, hyperplasia, cystic, glandular, multifocal	31 (91%)	30 (83%)	37 (90%)	40 (85%)
Endometrium, hyperplasia, cystic, reticulum cell, multifocal			1 (2%)	
HEMATOPOIETIC SYSTEM				
Blood		(1)		
Lymphocytosis		1 (100%)		
Bone marrow	(35)	(13)	(5)	(48)
Femoral, hyperplasia, neutrophil		3 (23%)	1 (20%)	
Femoral, hyperplasia, neutrophil, diffuse			1 (20%)	
Femoral, myelofibrosis	13 (37%)		1 (20%)	20 (42%)
Lymph node	(34)	(23)	(11)	(44)
Lumbar, hematopoietic cell proliferation				1 (2%)
Mediastinal, hyperplasia, lymphoid		1 (4%)		
Mediastinal, inflammation, acute		1 (4%)		
Mesenteric, hematopoietic cell proliferation		1 (4%)	4 (36%)	4 (9%)
Mesenteric, hematopoietic cell proliferation, multifocal				3 (7%)
Mesenteric, hyperplasia, lymphoid	1 (3%)			
Renal, hematopoietic cell proliferation				1 (2%)
Renal, hyperplasia, lymphoid	1 (3%)			
Lymph node, mandibular	(33)	(16)	(4)	(42)
Hyperplasia, lymphoid	1 (3%)	1 (6%)		2 (5%)
Pigmentation, diffuse	1 (3%)			

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7 (Continued)

	Untreated Control	Low Dose	Mid Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)				
Spleen	(34)	(26)	(17)	(47)
Depletion lymphoid				1 (2%)
Hemorrhage			1 (6%)	
Hyperplasia, lymphoid		1 (4%)		2 (4%)
Necrosis	1 (3%)		1 (6%)	
Red pulp, hematopoietic cell proliferation, diffuse	1 (3%)	8 (31%)	5 (29%)	5 (11%)
Thymus	(30)	(9)	(5)	(43)
Degeneration, acute	1 (3%)			
Inflammation, acute			1 (20%)	
INTEGUMENTARY SYSTEM				
Mammary gland	(33)	(6)	(7)	(40)
Hyperplasia, cystic	19 (58%)	2 (33%)		31 (78%)
Skin	(35)	(22)	(18)	(46)
Alopecia	5 (14%)	1 (5%)	7 (39%)	2 (4%)
Ulcer				1 (2%)
Sebaceous gland, hyperplasia				1 (2%)
Subcutaneous tissue, inflammation, chronic active				1 (2%)
MUSCULOSKELETAL SYSTEM				
Bone	(35)	(14)	(5)	(49)
Femur, hyperostosis				1 (2%)
Joint, tarsal, hyperostosis			1 (20%)	
NERVOUS SYSTEM				
Brain	(35)	(14)	(5)	(47)
Compression	1 (3%)			
Meninges, infiltration cellular, lymphocytic	6 (17%)			5 (11%)
RESPIRATORY SYSTEM				
Lung	(35)	(15)	(6)	(48)
Hyperplasia, lymphoid				2 (4%)
Alveolar epithelium, hyperplasia	1 (3%)			1 (2%)
Interstitium, inflammation, chronic active			1 (17%)	
Mediastinum, inflammation, acute			2 (33%)	
Nose	(35)	(14)	(5)	(48)
Glands, inflammation, acute, focal			2 (40%)	46 (96%)
Olfactory epithelium, metaplasia, focal	1 (3%)		2 (40%)	45 (94%)
SPECIAL SENSES SYSTEM				
Eye		(1)		
Atrophy		1 (100%)		
URINARY SYSTEM				
Kidney	(34)	(15)	(8)	(48)
Infarct				1 (2%)
Nephropathy, chronic	3 (9%)			3 (6%)
Glomerulus, amyloid deposition, diffuse		1 (7%)		
Glomerulus, inflammation, chronic, diffuse				1 (2%)
Renal tubule, dilatation		1 (7%)		
Renal tubule, regeneration	2 (6%)			5 (10%)
Urinary bladder	(34)	(12)	(5)	(47)
Dilatation		1 (8%)		

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

I. 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 viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both 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.

Fifteen $B6C3F_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at approximately 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

Hemagglutination Inhibition	Complement Fixation	ELISA
PVM (pneumonia virus of mice)	M. Ad. (mouse adenovirus)	MHV (mouse hepatitis virus)
Reo 3 (reovirus type 3)	LCM (lymphocytic choriomeningitis virus)	GDVII (24 mo)
GDVII (Theiler's encephalomyelitis virus) (6,12,18 mo)	Sendai (6 mo)	
Poly (polyoma virus)		
MVM (minute virus of mice)		
Ectro (infectious ectromelia)		
Sendai (12,18,24 mo)		

II. Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
6	--	None positive
12	1/9	PVM
	9/9	MHV
18	1/8	MVM
	1/8	MHV
Dowicide EC-7		
24	1/10	PVM
	2/6	MHV
Technical grade		
24	6/7	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers

APPENDIX F

FEED AND COMPOUND CONSUMPTION BY MICE IN THE TWO-YEAR FEED STUDIES OF PENTACHLOROPHENOL

TABLE F1. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Control		100 ppm				200 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
1	4	26.7	4	26.4	1.0	15	4	26.8	1.0	30
5	4	30.3	4	30.0	1.0	13	4	30.9	1.0	26
10	4	32.7	4	33.0	1.0	12	5	32.5	1.3	31
12	4	32.2	5	33.7	1.3	15	5	34.3	1.3	29
16	8	35.2	7	35.2	0.9	20	6	35.8	0.8	34
20	7	36.5	7	36.3	1.0	19	6	37.2	0.9	32
25	6	35.4	7	37.3	1.2	19	7	37.2	1.2	38
30	8	37.2	8	38.1	1.0	21	8	38.3	1.0	42
34	7	38.2	8	39.2	1.1	20	7	39.5	1.0	35
38	7	38.7	7	40.1	1.0	17	7	39.9	1.0	35
42	8	39.7	9	39.9	1.1	23	9	39.7	1.1	45
46	7	40.1	7	40.2	1.0	17	7	41.2	1.0	34
50	6	39.9	6	40.3	1.0	15	7	41.2	1.2	34
57	7	39.9	8	40.6	1.1	20	7	40.6	1.0	34
61	11	37.2	9	40.1	0.8	22	9	39.6	0.8	45
66	6	38.0	5	40.3	0.8	12	5	40.0	0.8	25
70	9	37.6	6	38.1	0.7	16	5	41.6	0.6	24
74	14	40.2	15	42.7	1.1	35	16	42.0	1.1	76
78	5	37.6	7	37.7	1.4	19	6	37.0	1.2	32
82	6	37.2	7	38.6	1.2	18	6	37.8	1.0	32
87	6	37.3	6	37.7	1.0	16	6	38.1	1.0	31
91	10	37.1	5	37.3	0.5	13	7	39.2	0.7	36
95	5	37.3	5	37.0	1.0	14	6	38.3	1.2	31
100	6	36.8	5	36.7	0.8	14	6	38.0	1.0	32
Mean	6.9	36.6	6.7	37.4	1.0	18	6.7	37.8	1.0	35
SD (d)	2.4		2.3		0.2	5	2.4		0.2	10
CV(e)	34.8		34.3		20.0	27.8	35.8		20.0	28.6

(a) Grams of feed removed from the feeder per animal per day; not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of technical-grade pentachlorophenol consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE F2. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF TECHNICAL-GRADE PENTACHLOROPHENOL

	Control		100 ppm				200 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
1	4	20 9	4	20 5	1 0	20	4	20 3	1 0	39
5	3	23 3	3	22 9	1 0	13	3	23 1	1 0	26
10	4	25 4	4	25 5	1 0	16	4	25 4	1 0	31
12	3	25 8	4	25 9	1 3	15	4	25 6	1 3	31
16	8	27 2	7	27 2	0 9	26	6	26 8	0 8	45
20	7	28 3	7	29 2	1 0	24	6	28 9	0 9	42
25	7	29 6	6	30 2	0 9	20	6	29 0	0 9	41
30	7	31 4	7	31 7	1 0	22	8	31 0	1 1	52
34	8	33 2	8	32 5	1 0	25	8	32 2	1 0	50
38	8	33 3	7	34 0	0 9	21	7	32 8	0 9	43
42	9	35 7	10	35 4	1 1	28	9	34 4	1 0	52
46	7	37 0	6	36 3	0 9	17	6	36 2	0 9	33
50	6	36 6	7	37 6	1 2	19	7	34 3	1 2	41
57	8	37 6	7	38 3	0 9	18	7	36 3	0 9	39
61	9	37 7	8	38 7	0 9	21	9	37 1	1 0	49
66	4	40 1	4	38 8	1 0	10	4	37 2	1 0	22
70	3	39 6	4	39 9	1 3	10	4	38 2	1 3	21
74	8	41 0	9	40 6	1 1	22	9	39 7	1 1	45
78	4	40 0	4	40 9	1 0	10	4	39 2	1 0	20
82	5	41 9	4	42 5	0 8	9	4	39 6	0 8	20
87	5	41 3	4	41 7	0 8	10	4	38 6	0 8	21
91	5	41 8	4	42 3	0 8	9	4	38 4	0 8	21
95	4	42 4	4	41 5	1 0	10	4	37 0	1 0	22
100	5	42 5	4	43 7	0 8	9	5	39 0	1 0	26
Mean	5 9	34 7	5 7	34 9	1 0	17	5 7	33 3	1 0	35
SD (d)	2 0		2 0		0 2	6	1 9		0 2	11
CV (e)	33 9		35 1		20 0	35 3	33 3		20 0	31 4

(a) Grams of feed removed from the feeder per animal per day, not corrected for scatter
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of technical-grade pentachlorophenol consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE F3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Control		100 ppm				200 ppm				600 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	Mid/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	4	29 7	4	29 5	1 0	14	4	29 6	1 0	27	4	29 2	1 0	82
10	4	32 5	4	32 0	1 0	13	4	32 0	1 0	25	5	31 7	1 3	95
13	7	32 8	6	33 5	0 9	18	6	33 9	0 9	35	7	33 1	1 0	127
18	8	35 5	7	35 0	0 9	20	7	35 2	0 9	40	7	34 5	0 9	122
22	6	36 1	7	36 0	1 2	19	7	35 6	1 2	39	6	35 5	1 0	101
28	7	37 2	7	36 2	1 0	19	8	36 8	1 1	43	8	36 4	1 1	132
32	7	38 2	8	36 5	1 1	22	8	37 7	1 1	42	7	37 2	1 0	113
36	6	38 1	7	37 4	1 2	19	7	38 2	1 2	37	7	36 6	1 2	115
40	8	39 1	8	39 1	1 0	20	8	39 0	1 0	41	9	36 6	1 1	148
45	7	39 3	6	38 6	0 9	16	7	38 6	1 0	36	7	36 6	1 0	115
49	4	38 1	5	35 5	1 3	14	6	37 6	1 5	32	5	36 3	1 3	83
53	7	39 5	6	37 3	0 9	16	7	37 4	1 0	37	7	36 6	1 0	115
57	5	39 9	5	38 4	1 0	13	6	37 5	1 2	32	6	37 3	1 2	97
60	6	39 6	7	38 0	1 2	18	9	37 6	1 5	48	8	36 4	1 3	132
65	7	37 1	8	38 2	1 1	21	8	37 7	1 1	42	8	32 8	1 1	146
71	15	38 9	15	37 4	1 0	40	15	37 4	1 0	80	14	37 2	0 9	226
76	4	38 2	4	35 6	1 0	11	4	36 4	1 0	22	6	36 0	1 5	100
80	6	37 8	6	35 8	1 0	17	6	36 2	1 0	33	7	35 7	1 2	118
84	6	37 8	6	36 5	1 0	16	6	37 2	1 0	32	8	35 1	1 3	137
89	7	39 3	6	35 0	0 9	17	6	35 3	0 9	34	8	36 7	1 1	131
93	5	36 4	5	35 5	1 0	14	5	36 2	1 0	28	6	35 8	1 2	101
97	5	36 4	5	33 8	1 0	15	6	34 7	1 2	35	6	34 9	1 2	103
101	6	36 2	6	35 5	1 0	17	6	35 0	1 0	34	5	35 3	0 8	85
Mean	6 4	37 1	6 4	35 9	1 0	18	6 8	36 2	1 1	37	7 0	35 4	1 1	118
SD (d)	2 3		2 2		0 1	6	2 2		0 2	11	2 0		0 2	30
CV (e)	35 9		34 4		10 0	33 3	32 4		18 2	29 7	28 6		18 2	25 4

(a) Grams of feed removed from feeder per animal per day, not corrected for scatter
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of pentachlorophenol, Dowicide EC 7, consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE F4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PENTACHLOROPHENOL, DOWICIDE EC-7

	Control		100 ppm				200 ppm				600 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	Mid/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	4	23 0	4	23 0	1 0	17	4	23 0	1 0	35	4	22 8	1 0	105
10	4	24 8	4	24 9	1 0	16	4	25 0	1 0	32	4	24 8	1 0	97
13	6	25 7	6	25 9	1 0	23	6	26 2	1 0	46	6	25 7	1 0	140
18	7	27 8	7	28 1	1 0	25	6	27 8	0 9	43	7	27 4	1 0	153
22	7	28 6	7	28 4	1 0	25	6	29 4	0 9	41	6	28 6	0 9	126
28	7	30 5	7	30 1	1 0	23	8	30 7	1 1	52	8	29 5	1 1	163
32	7	31 5	8	31 8	1 1	25	9	31 6	1 3	57	8	30 9	1 1	155
36	6	33 3	7	33 2	1 2	21	7	33 1	1 2	42	7	31 5	1 2	133
40	9	35 0	9	34 3	1 0	26	8	34 9	0 9	46	9	32 4	1 0	167
45	6	35 8	6	35 2	1 0	17	7	35 8	1 2	39	7	32 9	1 2	128
49	3	35 3	5	35 0	1 7	14	3	35 1	1 0	17	4	31 7	1 3	76
53	4	35 8	6	35 1	1 5	17	6	35 4	1 5	34	6	31 8	1 5	113
57	4	36 0	5	34 8	1 3	14	4	36 6	1 0	22	5	31 2	1 3	96
60	6	37 0	6	36 3	1 0	17	7	37 5	1 2	37	7	31 8	1 2	132
65	8	34 5	7	35 6	0 9	20	7	35 4	0 9	40	7	31 3	0 9	134
71	9	37 2	10	37 9	1 1	26	10	37 0	1 1	54	10	32 6	1 1	184
76	3	38 7	4	39 7	1 3	10	4	37 6	1 3	21	4	32 8	1 3	73
80	4	39 6	4	39 5	1 0	10	5	37 3	1 3	27	3	32 7	0 8	55
84	4	40 0	4	38 8	1 0	10	4	36 7	1 0	22	4	32 9	1 0	73
89	4	40 4	4	39 4	1 0	10	4	36 8	1 0	22	4	33 4	1 0	72
93	4	40 4	4	39 4	1 0	10	4	38 0	1 0	21	4	31 8	1 0	75
97	4	40 7	4	38 2	1 0	10	4	35 9	1 0	22	5	33 3	1 3	90
101	4	42 0	4	39 2	1 0	10	4	38 1	1 0	21	4	32 7	1 0	73
Mean	5 4	34 5	5 7	34 1	1 1	17	5 7	33 7	1 1	34	5 8	30 7	1 1	114
SD (d)	1 9		1 8		0 2	6	1 9		0 2	12	1 9		0 2	37
CV (e)	35 2		31 6		18 2	35 3	33 3		18 2	35 3	32 8		18 2	32 5

(a) Grams of feed removed from feeder per animal per day, not corrected for scatter
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of pentachlorophenol, Dowicide EC 7, consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX G

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

Meal Diet: March 1982 to April 1984

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE G1. 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 ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.08 ± 1.19	21.2-25.9	26
Crude fat (percent by weight)	59 ± 0.46	4.2-5.8	26
Crude fiber (percent by weight)	3.49 ± 0.36	2.8-4.5	26
Ash (percent by weight)	6.64 ± 0.23	6.23-7.11	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	11,596 ± 4,203	4,200-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	19.08 ± 4.16	12.0-31.0	26
Riboflavin (ppm)	7.6 ± 0.85	7.58-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.25 ± 0.10	1.04-1.43	26
Phosphorus (percent)	0.98 ± 0.05	0.87-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE G4 CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0 51 ± 0 14	0 18 0 74	26
Cadmium (ppm) (a)	0 11 ± 0 03	0 10 0 20	26
Lead (ppm)	0 79 ± 0 62	0 33 3 37	26
Mercury (ppm) (b)	<0 05		26
Selenium (ppm)	0 31 ± 0 06	0 22 0 45	26
Aflatoxins (ppb) (b)	<5 0		26
Nitrate nitrogen (ppm) (c)	9 25 ± 4 09	2 50 18 0	26
Nitrite nitrogen (ppm) (c)	1 73 ± 1 67	0 10 6 10	26
BHA (ppm) (d)	4 23 ± 4 93	2 0 20 0	26
BHT (ppm) (d)	2 83 ± 2 58	1 0 13 0	26
Aerobic plate count (CFU/g) (e)	137,427 ± 133,363	6,200 420,000	26
Coliform (MPN/g) (f)	695 0 ± 911 0	3 0 2,400	26
E coli (MPN/g)	10 9 ± 30 0	3 0 150	26
Total nitrosamines (ppb) (g)	5 15 ± 5 9	0 8 30 30	26
N Nitrosodimethylamine (ppb) (g)	4 38 ± 5 95	0 5 30 0	26
N Nitrosopyrrolidine (ppb) (g)	0 78 ± 0 60	0 3 2 10	26
Pesticides (ppm)			
α BHC (b,h)	<0 01		26
β BHC (b)	<0 02		26
γ BHC Lindane (b)	<0 01		26
δ BHC (b)	<0 01		26
Heptachlor (b)	<0 01		26
Aldrin (b)	<0 01		26
Heptachlor epoxide (b)	<0 01		26
DDE (b)	<0 01		26
DDD (b)	<0 01		26
DDT (b)	<0 01		26
HCB (b)	<0 01		26
Mirex (b)	<0 01		26
Methoxychlor (b)	<0 05		26
Dieldrin (b)	<0 01		26
Endrin (b)	<0 01		26
Telodrin (b)	<0 01		26
Chlordane (b)	<0 05		26
Toxaphene (b)	<0 1		26
Estimated PCBs (b)	<0 2		26
Ronnel (b)	<0 01		26
Ethion (b)	<0 02		26
Trithion (b)	<0 05		26
Diazinon (b)	<0 1		26
Methyl parathion (b)	<0 02		26
Ethyl parathion (b)	<0 02		26
Malathion (i)	0 14 ± 0 17	<0 05 0 81	26
Endosulfan I (b)	<0 01		26
Endosulfan II (b)	<0 01		25
Endosulfan sulfate (b)	<0 03		26

(a) Two lots contained more than 0 10 ppm
(b) All values were less than the detection limit, given in the table as the mean
(c) Source of contamination alfalfa, grains, and fish meal
(d) Source of contamination soy oil and fish meal
(e) CFU = colony forming unit
(f) MPN = most probable number
(g) All values were corrected for percent recovery
(h) BHC = hexachlorocyclohexane or benzene hexachloride
(i) Fourteen batches contained more than 0 05 ppm

APPENDIX H

METHODS USED IN SIX-MONTH SUPPLEMENTAL FEED STUDIES OF PENTACHLOROPHENOL

I. Behavioral Studies

Behavioral studies were carried out on the 10 males and 10 females from each dosed group designated for behavior, histopathology, and clinical chemistry studies (core group). Ten controls of each sex also were examined. Female mice were studied during the period July 7-11, 1982, after 4 weeks of chemical exposure and again during the period December 1-5, 1982, after 25 weeks of chemical exposure. Male mice were studied on July 14-18, 1982, and again on December 8-12, 1982.

Before initiation of the studies, the 52 cages of five mice each were randomly sorted to provide an unbiased study order during the 2-week study period. The order was different for each sex, but the same order was used when studies were repeated after 25 weeks of chemical exposure. Cage identification was coded before the study, so that the behavioral evaluations were performed "blind." Animals were transferred to clean cages on a clean rack and moved within the animal housing facility to the behavioral study laboratory, where they remained for a minimum of 1 hour before initiation of the studies.

Mice were initially examined for the presence or absence of autonomic signs. Specific attention was given to tremors, exophthalmos, and piloerection in undisturbed animals and to diarrhea, lacrimation, nasal discharge, salivation, urinary incontinence, and alopecia in restrained animals. Pinnal, corneal, and acceleration-righting reflexes were evaluated, and other abnormalities were recorded as observed.

Spontaneous motor activity was recorded with a Proximity Sensor (Columbus Instruments, Columbus, Ohio), which measures changes in electrical capacitance produced by animal movement. Activity counts were fed directly into a printout counter, and totals were recorded for the last 5 minutes of the 6-minute session. The first minute of each session was used as an accommodation period.

For measurement of motor activity and startle response, the animals were placed in a clean, dry, 1,000-ml beaker within an Industrial Acoustics AC-1 sound-isolating chamber. A white-noise mask was used to provide uniform background sound.

Acoustical startle response, measured with a Respondex A startle monitoring device (Columbus Instruments), began immediately after measurement of motor activity. Ten startle stimuli (the minimum number) were presented to each animal. Each stimulus was a 200-msec, 7.0-kHz sound pulse at 123 db. The magnitude of response was recorded after each stimulus. Responses were not recorded when animal movement immediately preceded the stimuli.

The presence or absence of visual-placement response was evaluated by lowering the animal by the tail to the grip ring of the grip strength monitor and observing whether the animal extended its forelimbs in a placing response. The animal was allowed to grip the ring of the device (similar to the method described by Meyer et al., 1979) and then was pulled away smoothly and steadily until it released the ring. Maximum force exerted was recorded from a Chatillon gauge attached to the ring. This procedure was repeated until three valid measurements were obtained. The average of these measurements was recorded as the grip strength for that animal.

Animals then were placed on a 2.5-cm diameter rod (rotarod) rotating at 12 rpm and elevated 38 cm above plastic cages containing bedding material. Three animals were trained and tested simultaneously. Training consisted of a 2-minute learning period during which the animals were replaced on the rod as often as necessary. The mice then were removed for rectal temperature measurement and returned for testing on the rota-rod approximately 3 minutes later. During testing, animals were placed on the rod, and the time each animal remained on the rod (up to a maximum of 2 minutes) was recorded.

Rectal temperature was recorded with the Baily Instruments BAT-8 digital thermometer. The rectal probe, suitable for small rodents, was coated with sterile surgical lubricant before insertion.

II. Hematologic Analyses

Blood collection: Blood samples for hematologic evaluation were obtained from the orbital plexus. Free-flowing capillary blood was collected directly into Microtainer capillary whole blood collector tubes (Becton-Dickinson) containing EDTA as an anticoagulant.

Erythrocyte, leukocyte, and platelet counts and hematocrit: Whole blood was aspirated and counted after automatic dilution on an Ortho ELT-8 laser hematology counter.

Differential leukocyte count: The differential leukocyte count expresses in percent the relative number of the various types of leukocytes present in the peripheral blood. One hundred leukocytes were identified from a blood smear stained with a modified Romanowsky stain on a Hema-Tek® slide stainer. If present, nucleated erythrocytes were reported.

Reticulocyte count: Erythrocytes were stained with a vital stain (new methylene blue), and a smear was prepared with the erythrocyte/stain mixture. The number of reticulocytes per 1,000 erythrocytes was expressed as the percentage of erythrocytes.

Hemoglobin: Blood was diluted with a solution of cyanide ferricyanide, the erythrocytes were lysed, and the hemoglobin was converted to cyanomethemoglobin which was determined spectrophotometrically with appropriate standards at 540 nm on an Ortho ELT-8 laser hematology counter.

III. Clinical Chemical Analyses

γ-Glutamyl transpeptidase: γ-Glutamyl transpeptidase activity was measured by a modification of the method of Szasz (1969). The assay was performed at 30° C on a Gemsaec centrifugal analyzer with reagents prepared by SmithKline Instruments, Inc. (Sunnyvale, California).

Alkaline phosphatase: The assay, modified by Wilkinson et al. (1969), was performed at 30° C in a Gemsaec centrifugal analyzer with spectrophotometric detection at 405 nm and reagents prepared by SmithKline Instruments, Inc.

Total protein: Total protein was determined by reacting samples with cuprous ions in an alkaline solution (Henry et al., 1974). The procedure was performed on a Gemsaec centrifugal analyzer.

Creatinine: Serum creatinine was determined according to the procedure of Jaffe (1886) as modified by Slot (1965). Analyses were performed on a Gemsaec centrifugal analyzer with "Spin-Chem" reagents.

Serum glutamic-oxaloacetic transaminase: The kinetic assay, based on the method of Karmen (1955) as modified by Henry et al. (1960), was performed at 30° C with a Gemsaec centrifugal analyzer and reagents prepared by SmithKline Instruments, Inc.

Serum glutamic-pyruvic transaminase: The kinetic assay, based on the method of Wroblewski and LaDue (1956) as modified by Henry et al. (1960), indirectly measures the formation of pyruvic acid from alanine. The procedure was performed at 30° C with a Gemsaec centrifugal analyzer and reagents prepared by SmithKline Instruments, Inc.

Cholesterol: Performed according to the method of Allain et al. (1974), this spectroscopic procedure was based on the oxidation of cholesterol by cholesterol oxidase, producing hydrogen peroxide, which in turn reacts with 4-aminoantipyrine and phenol. The assay was performed with a Gemsaec centrifugal analyzer with "Spin-Chem" reagents.

IV. Urinalyses

The following urinalyses were performed on urine samples that were collected by cage from mice in the core group during study weeks 9 and 26:

Color: The color of each sample was described.

Specific gravity: Urine samples were read directly on an American Optical refractometer/total solids meter.

Urinary creatinine: Urinary creatinine was determined according to the method of Jaffe (1886) as modified by Slot (1965). Analyses were performed with the Gemsaec centrifugal analyzer and "Spin-Chem" reagents after samples had been diluted 1:10 to bring the concentration within the range of linearity of the procedure (Henry et al., 1974).

V. Histopathologic Examinations

A detailed necropsy was performed on all mice in the core group. A histologic examination was performed on all mice that died during the studies, all high dose and control animals, and the 600-ppm groups receiving technical-grade pentachlorophenol. Selected tissues from other groups were examined.

The following histochemical stains were applied to sections of liver, kidney, and urinary bladder from two to four animals per group: Ziehl Nielson's acid fast, Gomori's stain for iron, McManus PAS, Hall's stain for bilirubin, and Stein's stain for bile pigments. Oil-Red-O and Nile Blue Sulfate stains were applied to the liver only.

Methods used for histochemical stains were as follows:

Ziehl Nielson's acid fast: Tissues were formalin-fixed, paraffin-embedded, and counterstained in methylene blue (Luna, 1968) or picric acid.

Stein's stain for bile pigment: Formalin-fixed, paraffin-embedded tissues were used for the stain, which was based on the use of iodine for oxidation of bile pigments to biliverdin (Sheehan and Hrapchak, 1980).

Hall's stain for bilirubin: Formalin-fixed, paraffin-embedded tissues were used for the stain, which was based on the conversion of bilirubin to biliverdin (Sheehan and Hrapchak, 1980).

Gomori's stain for iron: Formalin-fixed, paraffin-embedded tissues were used for the stain, which includes potassium ferrocyanide and Kernechtrot counterstain (Sheehan and Hrapchak, 1980).

PAS: Formalin-fixed, paraffin-embedded tissues were used for the staining procedure (Sheehan and Hrapchak, 1980).

Oil-Red-O: Formalin-fixed, frozen sections were used for the staining procedure (Luna, 1968).

Nile Blue Sulfate: Formalin-fixed, frozen sections were used for the staining procedure (Lillie and Fullmer, 1968).

VI. Biochemical Analyses

Aryl hydrocarbon hydroxylase, cytochrome P450, oxidative phosphorylation, and porphyrins: Mice analyzed for aryl hydrocarbon hydroxylase (AHH), cytochrome P450, and uncoupling of oxidative phosphorylation were killed by decapitation. The liver, minus gallbladder, was removed, rinsed in ice-cold 0.25 M sucrose, and homogenized in 0.25 M sucrose (3:1 volume sucrose solution:liver weight) with a Potter-Elevehjem glass homogenizer. Because of the large number of liver samples to be analyzed, it was not feasible to kill all the mice on the same day; therefore, the termination order was randomized according to dose group.

Four control mice used for AHH determination were administered 1 mg of 3,4-benzo[*a*]pyrene by intraperitoneal injection 24 hours before they were killed. These mice served as a positive control for induction of liver enzymes.

Mitochondrial and microsomal cell fractions were prepared from the liver homogenates. All centrifugations were performed at 0°-4° C. Mitochondria were obtained by first centrifuging the liver homogenates at 600 × *g* for 10 minutes in a clinical centrifuge to precipitate the cell membrane and nuclear debris and then centrifuging the supernatant in a Sorvall RC2-B centrifuge at 10,000 × *g*. The precipitated mitochondria were washed once with 0.25 M sucrose and recentrifuged at 10,000 × *g*; this precipitate was washed with 0.25 M sucrose and resuspended in a volume of 0.25 M sucrose equal to three times the original weight of the liver. The mitochondrial suspensions were stored under nitrogen in sealed vessels at −20° C until analysis.

To obtain microsomes, the supernatant from the first 10,000 × *g* centrifugation was centrifuged for 1 hour at 104,000 × *g* in a Beckman model L5-65 ultracentrifuge. The microsomal pellet was resuspended in a volume of 0.25 M sucrose equal to the original weight of the liver. The microsomal suspensions were analyzed within 48 hours for AHH activity and cytochrome P450 concentrations.

The concentration of protein in the mitochondrial and microsomal suspensions was determined (Lowry et al., 1951) before assays were performed. AHH activity of the microsomal preparation (Gielen et al., 1972) was measured in a 1.00-ml reaction mixture that contained 50 µmol of potassium phosphate buffer (pH 7.2), 0.36 µmol of NADPH, 0.39 µmol of NADH, 600 µg of bovine serum albumin, 3 µmol of magnesium chloride, and 0.10 ml of microsomes (containing 300 µg of microsomal protein). The substrate 3,4-benzo[*a*]pyrene (80 nmol) was added in 40 µl of methanol just before a 10-minute incubation at 37° C. The reaction was terminated by adding 1.0 ml of cold acetone and 3.25 ml of hexane. The samples were reincubated at 37° C for 10 minutes to extract the 3,4-benzo[*a*]pyrene and its metabolites. A 1.0-ml aliquot from the 3.25-ml organic phase was extracted with 3.0 ml of 0.1 N sodium hydroxide. The extract was analyzed for fluorescence with an activation peak at 396 nm and emission maximum at 522 nm. The fluorescence of a blank sample, to which the 3,4-benzo[*a*]pyrene was added after incubation and addition of acetone, was subtracted from each experimental sample. The amount of fluorescence of duplicate samples was averaged; this average represented the unit activity of AHH per milligram of protein. (A unit of AHH activity was defined as that amount of enzyme catalyzing the formation of hydroxylated product per minute at 37° C causing fluorescence equivalent to that of 1 pmol of 3-hydroxybenzo[*a*]pyrene.)

Cytochrome P450 concentration in the microsomes was measured by its dithionite difference spectrum in an Aminco DW-2 split-beam recording spectrophotometer (Omura and Sato, 1964). Three milliliters of microsomes (containing 1 mg protein/ml 0.1 M potassium phosphate buffer, pH 7.4) was added to both the sample and reference cuvette. A minimum amount of solid sodium dithionite was added to each cuvette, the cuvettes were shaken by inversion, and a baseline for the sample and reference cuvettes was established. Carbon monoxide was bubbled into the sample cuvette for 10 seconds, and the spectrum difference was recorded. Differences in absorption between the Soret maximum at 448-450 nm and 490 nm were calculated with an extinction coefficient of 91 $mM^{-1}cm^{-1}$.

The effect of pentachlorophenol on mitochondrial oxidative phosphorylation was determined by a modified method of Friedman et al. (1977) in a YSI Model 53 biological oxygen monitor with a Clark fixed-voltage polarizing probe. The reaction chamber contained the following in a total volume of 3.6 ml: 0.33 M mannitol, 0.33 mM EDTA, 3.5 mM potassium chloride, 3.5 mM potassium phosphate, 4.8 mg bovine serum albumin, and 4.0 mg mitochondrial protein. To this reaction mixture was added one of the following:

Substrate A: 1.4 mM citrate + 0.14 mM ADP + 0.14 mM NAD
Substrate B: 1.4 mM citrate + 0.14 mM ADP + 0.14 mM NADP
Substrate C: 1.4 mM pyruvate + 0.14 mM ADP

The final pH of the incubation mixture was 7.4. Oxygen uptake was measured in all samples at 30° C after an incubation of 15 minutes. Calculations were performed as follows:

1. 56.304 µl of air (33.6% oxygen) present in 3.6 ml of sample at 30° C: equivalent to (56.304) × (0.336) = 18.92 µl oxygen in a 3.6-ml sample.

2. Readings were taken four times per hour.

3. Readings were divided by the 4 mg of protein present.

4. Therefore, Q_{O_2} = percent change in saturation × 18.92 = µl oxygen /mg protein/h.

P:O ratios were defined as the moles of ADP divided by the moles of oxygen used. A 3.6-ml sample with 8.08 µmol of oxygen used 0.503 µmol ADP; therefore, the

$$\text{P:O ratio} = \frac{0.503\ \mu\text{mol ADP}}{(8.08) \times (\text{percentage drop in saturation})}$$

Liver and urine porphyrins: The mice analyzed for liver porphyrins were killed by an intraperitoneal overdose injection of sodium pentobarbital, and the liver (minus gallbladder) was removed. An aliquot of liver was set aside for histologic examination, and the remainder was assayed for total liver porphyrins by a slightly modified method of Abbritti and DeMatteis (1971-1972). A weighed portion of liver was stored at −20° ± 2° C until analysis. The liver aliquot was homogenized in 20 volumes of 0.9 N perchloric acid:ethanol (1:1) and centrifuged for 30 minutes in a clinical centrifuge at 700 × *g*. One milliliter of the supernatant was diluted to 10 ml, and its fluorescence was determined in an AMINCO SPF-500 spectrofluorometer with an excitation wavelength of 400 nm and fluorescence recording at an emission wavelength of 600 nm. The concentration of liver porphyrins was determined from a linear regression curve, developed by spiking representative liver samples of different concentrations with a 5-ng uroporphyrin standard.

Urine to be analyzed for porphyrins was collected by cage from groups of five mice. Coproporphyrins and uroporphyrins were analyzed in urine by the UV spectrophotometric method of Henry et al. (1974). Calculations were made with the following formula:

$$A_{corr} = \frac{2A_{max} - (A_{380} + A_{430})}{K}$$

where:

K = 1.835
A_{corr} = 0.673 for 1 µg/ml
A = absorption

then:

$$\text{nmol porphyrin/ml urine} = \left[\frac{\frac{2A_{max} - (A_{380} + A_{430})}{1.835}}{0.673}\right] \times \left(\frac{\text{Extract volume}}{\text{Aliquot volume}}\right) \times \left(\frac{\text{nmol}}{\text{µg porphyrin/nmol}}\right)$$

VII. Immunologic Analyses

A. Assay for mitogen responses

1. Materials for assay

a. Eagle's Minimum Essential Medium (MEM) (Grand Island Biological Co.). Supplemented with 5% (v/v) heat-inactivated bovine calf serum (Colorado Serum Co.), 100 µg/ml penicillin, and 100 µg/ml streptomycin (Grand Island Biological Co.). Abbreviated M5. Stored at 4°-8° C.
b. MEM supplemented with 20% (v/v) heat-inactivated bovine calf serum, 100 µg/ml penicillin, and 100 µg/ml streptomycin. Abbreviated M20. Stored at 4°-8° C.
c. Hanks' Balanced Salt Solution (HBSS). Prepared in 500-ml lots by combining 50 ml of tenfold concentrated HBSS (Grand Island Biological Co.) with 450 ml of sterile distilled water. Stored at 4°-8° C.
d. Phytohemagglutinin-P (PHA) (DIFCO Laboratories) at 20 µg/ml in M5. Stored at ≤ −10° C.
e. Concanavalin A (Con A) (Miles-Yeda, Ltd.) at 20 µg/ml in M5. Stored at ≤ −10° C.
f. Con A (as above) at 10 µg/ml in M5. Stored at ≤ −10° C.
g. Pokeweed Mitogen (PWM) (Grand Island Biological Co.) diluted 1:101 in M5. Stored at ≤ −10° C.
h. Lymphocyte Separation Medium (LSM) (Bionetics Lab Products). Stored at room temperature.
i. [Methyl-^{3}H]Thymidine (Amersham-Searle). Specific activity of 5 Ci/mmol, diluted to 10 µCi/ml in M5. Stored at 4°-8° C.
j. OCS scintillation fluid (Amersham-Searle). Stored at room temperature.

2. Stock reagents

a. MEM. Powdered medium and incomplete (i.e., serumless) medium. Stored at 4°-8° C.
b. Penicillin-streptomycin Solution (Grand Island Biological Co.). Stored at ≤ −10° C.
c. Tenfold concentrated HBSS. Stored at 4°-8° C.
d. Con A. Stored at room temperature.
e. PHA. Stored at 4°-8° C.

f. PWM. Stored at 4°-8° C.
g. Bovine calf serum. Stored at ≤ −10° C.

3. Preparation of suspensions

a. Lymphoid cell suspensions

(1) Animal was killed by cervical dislocation.
(2) Animal was pinned to the dissecting board ventral side up. The animal pelt was saturated with 95% ethanol.
(3) Instruments were immersed in absolute ethanol and flamed before an incision was made. Note: Instruments were flamed and cooled before the removal of each organ.
(4) An incision was made midline on the abdomen extending from the throat area to the groin. The skin was retracted and pinned.
(5) An incision was made through the peritoneal wall from the throat to the groin.
(6) The thymus, without parathymic nodes, was removed and placed in a 50-ml conical tube containing cold M20.
(7) The spleen was pulled free from the mesenteric tissue and placed in a 50-ml conical tube containing cold M20.
(8) The thymus and spleen were gently homogenized one at a time with sterile tissue grinders until the capsules or connective tissues were clear.
(9) Cell suspensions were passed through a sterile copper screen into a 50-ml conical tube.

b. Spleen cell suspensions: Homogenized and screened spleen cell suspensions were diluted to approximately 14 ml with cold M20. Spleen mononuclear cells were separated by layering 6 ml of LSM solution below the spleen cell suspension and centrifuging for 6 minutes at approximately 2,700 rpm. After centrifugation, the top 8 ml from each LSM preparation was discarded. The remaining lymphocyte-rich fluid was withdrawn to within approximately one-fourth inch above the red blood cell pellet. Cells were washed three times in cold HBSS and resuspended in M5 at 5×10^6 viable, nucleated cells/ml.
c. Thymus cell suspensions: Thymus cell suspensions were processed simultaneously with spleen cell suspensions. Homogenized and screened thymus cell suspensions were washed once in cold HBSS and resuspended in M5 at 5×10^6 viable, nucleated cells/ml.
d. Additional guidelines

(1) All cell preparations were stored on ice or refrigerated when not in use.
(2) All media were stored cold.
(3) Media were not allowed to turn basic. Bottles were tightly capped.
(4) All washed cell suspensions were centrifuged for 10 minutes at 1,000 rpm.

4. Preparation of mitogens and culture plate

The culture plate(s) were prepared in a horizontal flow hood not used for animal work.

a. Mitogen stocks were thawed at room temperature.
b. A Falcon microtest II culture plate was aseptically removed from its plastic sleeve. A Falcon microtest lid was immediately removed from its plastic sleeve and placed correctly on the plate.

c. A top row ("A") and a complete row immediately below experimental and control rows were filled with 0.2 ml of incomplete MEM per well. There were four wells for each culture or control. Plate lids were labeled with the assay date and project number.

Controls:
0.2 ml M5
0.2 ml Con A
0.2 ml PHA
0.2 ml PWM

Cultures:
0.1 ml cells + 0.1 ml M5
0.1 ml cells + 0.1 ml Con A
0.1 ml cells + 0.1 ml PHA
0.1 ml cells + 0.1 ml PWM

Thymus cells were cultured with Con A (20 µg/ml) and PHA (20 µg/ml). Spleen cells were cultured with PHA (20 µg/ml), Con A (10 µg/ml), and PWM (1:101).

d. Plate(s) were placed in a humidified 37° ± 0.5° C incubator with 10% ± 0.5% carbon dioxide as soon as reagents were placed in wells. Plates were incubated a total of 72 hours (±3 hours).

5. Pulsing

a. [^{3}H]Thymidine stock solution (0.1 ml at 1 mCi/ml) was withdrawn, added to 9.9 ml M5 (final concentration 10 µCi/ml), and mixed thoroughly.
b. Control and experimental wells were pulsed with 1 µCi [^{3}H]thymidine in 0.1 ml solution for 48 hours (±3 hours) after cells were added to plates.
c. Plates were replaced in incubator for final 24 hours.

6. Harvesting

a. Plate(s) were harvested with a cleaned mash unit 72 hours (±3 hours) after cells were added.
b. Filter paper strips were dried for at least 20 minutes under hot lights, and forceps were used to place filter "circles" in minivials containing 3 ml of OCS scintillation fluid. Vials were counted in a liquid scintillation counter.

B. Hemagglutination assay

1. Materials

a. Dulbecco's phosphate buffered saline (PBS). Stored at room temperature.
b. PBS supplemented with 0.1% (v/v) heat-inactivated (56° C for 30 minutes) normal rabbit serum (Grand Island Biological Co.). Abbreviated PBS-NRS; stored at 4°-8° C.
c. PBS-NRS supplemented with 2-mercaptoethanol (2-ME) (Eastman Kodak Co.) to give a final concentration of 0.2 M 2-ME. Abbreviated PBS-NRS-2-ME; stored at 4°-8° C.
d. Sheep erythrocytes (SRBC) (Granite Diagnostics, Inc.) washed with PBS as described in methods for plaque test below and prepared as a 2% (v/v) suspension in PBS. Stored at 4°-8° C.

e. Microtiter equipment (Dynatech Laboratories, Inc.):

Disposable U plates
25-µl Microdiluters
25-µl Pipet droppers
25-µl "Go-No-Go" testers

2. Methods

a. A 25-µl pipette dropper was used to add 25 µl PBS-NRS to each well of a microtiter test plate, allowing for one row of 12 wells for each serum sample to be tested.
b. A 25-µl pipette dropper was used to add 25 µl PBS-NRS-2-ME to each well of a separate test plate, allowing for one row of 12 wells for each serum sample to be tested.
c. Each serum sample was diluted 1:10 in PBS-NRS. The 1:10 dilutions were tested for total antibody (PBS-NRS), and undiluted serum samples were tested for 2-ME-resistant antibodies.
d. The 25-µl microdiluters were rinsed in distilled water, heated to glowing red in an open flame, and cooled to room temperature. Immediately before use, the cooled microdiluter was dipped in distilled water and blotted on the microtiter 25-µl "Go-No-Go" test strip. A cooled diluter was used to transfer 25 µl of the 1:10 dilution of test serum to the well of column 1, row A, of the PBS-NRS test plate. The diluter was left in the well. This procedure was repeated with another test serum until all column-1 wells of all eight rows contained test serum; samples were diluted as described in the instruction manual.
e. The above procedure was repeated with the undiluted serum samples and the test plates that contained PBS-NRS-2-ME as a diluent.
f. A 25-µl pipette dropper was used to transfer 25 µl of the 2% SRBC suspension to each well of each test plate. Each plate was gently tapped at the edge 5-10 times to thoroughly mix the contents.
g. Each plate was sealed with sealing tape and incubated at 37° C for 1-3 hours.
h. The hemagglutination titer (i.e., reciprocal of the last dilution of test serum with a positive hemagglutination reaction) was read and recorded.
i. Plates were covered and incubated overnight in the refrigerator at 2°-8° C.
j. Plates were allowed to come to room temperature. Hemagglutination titers were read and recorded.

C. IgG hemolytic plaque test

1. Materials and reagents

a. SRBC: 50% packed in Alsever's (Granite Diagnostics, Inc.). Stored at 4°-8° C.
b. Agarose (Miles Laboratories, Inc.). Stored at 4°-8° C.
c. Tenfold concentrated HBSS (laboratory-prepared, 7/80) (diluted with distilled water before use). Stored at 4°-8° C.
d. Rabbit anti-mouse IgG serum, lyophilized (Cappel Laboratories). Stored at 4°-8° C.
e. Guinea pig complement, lyophilized (Grand Island Biological Co.). Stored at ≤10° C.
f. Guinea pig complement restoring solution (Grand Island Biological Co.). Stored at 4°-8° C.
g. MEM; powdered medium and incomplete (i.e., serumless) medium. Stored at 4°-8° C.
h. Penicillin-streptomycin solution. Stored at ≤10° C.
i. Bovine calf serum. Stored at ≤10° C.
j. 60 mm × 15 mm sterile petri dish, Falcon (Fisher Scientific Co.).

k. 16 mm × 125 mm borosilicate disposable culture tubes (Fisher Scientific Co.).
l. LSM (Litton Bionetics Lab Products). Stored at room temperature.

2. Immunization

The $B6C3F_1$ mice to be assayed for plaque-forming cells were immunized with SRBC 9 days before testing.

a. SRBC were used within 2 weeks of receipt.
b. An aliquot was withdrawn aseptically and centrifuged at 1,200 rpm on a CENTRA 7R IEC centrifuge. The supernatant was aspirated and discarded, and the pellet was resuspended in room-temperature HBSS (diluted 1:10); wash procedure was repeated two additional times.
c. One milliliter of packed SRBC was withdrawn with a 1.0-ml pipet, combined with 1.0 ml of room-temperature HBSS (diluted 1:10), and gently resuspended.
d. Cell concentration was measured with a hemacytometer, after a 10^{-5} dilution.
e. A suspension of 10^{10} SRBC/ml of HBSS was made, and 0.5 ml (5×10^9 SRBC) was injected intraperitoneally.

3. Assay preparations

a. Base pours

(1) A 2.4% solution of agarose in distilled water (w/v) was autoclaved for 20 minutes on slow exhaust and held in a 47° ± 2° C water bath to prevent gelling.
(2) HBSS (diluted 1:5) was prepared aseptically by combining 100 ml of tenfold concentrated HBSS with 400 ml of distilled water. The twofold concentrated HBSS was prepared up to 7 days before use and stored at 4°-8° C.
(3) Equal volumes of 2.4% agarose and warmed HBSS (47° ± 2° C; diluted 1:5) were combined to form a 1.2% agarose mixture. The mixture was gently swirled, the pH was adjusted with 7.5% sodium bicarbonate (0.5 ml/500 ml), and the mixture was stored at 47° ± 2° C until poured.
(4) Two milliliters of the 1.2% agarose was aliquoted to each 60-mm petri dish and immediately swirled to cover the dish bottom.
(5) The plates were allowed to gel for at least 15 minutes at room temperature and were placed in a humidified chamber containing 5% ± 0.5% carbon dioxide at 37° ± 5° C before assay.

b. Agarose tubes

(1) A 1.2% suspension of agarose in distilled water (w/v) was autoclaved for 20 minutes on slow exhaust and held in a 47° ± 2° C water bath to prevent gelling.
(2) Twofold concentrated HBSS was prepared as for the 2.4% agarose base pours.
(3) Equal volumes of 1.2% agarose and warmed twofold concentrated HBSS (47° ± 2° C) were combined, forming a 0.6% agarose mixture. The mixture was gently swirled, and its pH was adjusted with 7.5% sodium bicarbonate (0.5 ml/500 ml). It was stored at 47° ± 2° C until aliquots were taken.
(4) Two milliliters of the 0.6% agarose was placed in each 16 × 125 mm, prewarmed glass culture tube.
(5) Tubes were placed in a 47° ± 2° C water bath until ready for pouring.

c. Complement absorption

(1) SRBC were washed as described in the immunization procedure.
(2) Lyophilized guinea pig complement was reconstituted with cold guinea pig complement-restoring solution, mixed gently, and kept on ice continuously.
(3) When complement was dissolved, 1 ml of washed, packed SRBC was added per 10 ml of reconstituted complement. The complement-SRBC mixture was incubated for 60 minutes in an ice bath and was inverted at 10-minute intervals to maintain the suspension.
(4) After incubation, the SRBC were pelleted for 10 minutes at 1,500 rpm (4° ± 2° C) in an IEC CENTRA 7R centrifuge. The complement was withdrawn, placed in a clean tube, and spun again for 5 minutes at 2,500 rpm (4° ± 2° C).
(5) The complement was withdrawn, aliquoted to sterile 16 × 125 mm tubes, and frozen at ≤ 10° C.

d. Anti-mouse IgG preparation

(1) Lyophilized rabbit anti-mouse IgG was reconstituted with distilled sterile water, gently mixed until dissolved, and stored at 4°-8° C.
(2) A 1:800 (v/v) dilution of anti-mouse IgG in HBSS (diluted 1:10) was made and held at 4°-8° C for not more than 1 week before assay.

e. Calf serum absorption

(1) SRBC were washed as described in the immunization procedure.
(2) One milliliter of washed, packed SRBC was added per 10 ml of heat-inactivated calf serum to be absorbed. The serum-SRBC mixture was incubated for 60 minutes in an ice bath and inverted at 10-minute intervals.
(3) After incubation, the SRBC were pelleted for 10 minutes at 1,500 rpm at 4° ± 2° C in an IEC CENTRA 7R centrifuge. The serum was withdrawn, placed in a clean tube, and spun again for 5 minutes at 2,500 rpm at 4° ± 2° C.
(4) The serum was withdrawn, placed in sterile 16 × 125 mm tubes, and frozen at ≤ −10° C.

4. Preparation of lymphoid cell suspensions

a. The animal was anesthetized with ether. Blood was obtained by cardiac puncture and placed in a capillary blood serum separator tube (Becton-Dickinson Microtainer) and spun in a Beckman Microfuge at approximately 8,000 × *g* for 1-1/2 minutes. Serum was decanted into sterile test tubes and held at −20° C until tested for hemagglutination titer.
b. The animal was pinned to dissecting board, ventral side up; the animal pelt was saturated with 95% ethanol.
c. Instruments were immersed in absolute ethanol and flamed before an incision was made. Note: Instruments were flamed and cooled before removal of each organ.
d. An incision was made midline on the abdomen and extended from the throat area to the groin. The skin was retracted and pinned.
e. An incision was made through the peritoneal wall from the throat to the groin.
f. The spleen was pulled free from the mesenteric tissue and placed in a 50-ml conical tube containing cold M20.
g. Spleens were gently homogenized one at a time with sterile tissue grinders until capsules or connective tissues were clear.

h. Cell suspensions were passed through a sterile copper screen into a 50-ml conical tube.
i. The homogenized and screened spleen cell suspension was diluted to approximately 14 ml with cold M20. Spleen mononuclear cells were separated by layering 6 ml of LSM solution below the spleen cell suspension and centrifuging for 6 minutes at approximately 2,700 rpm. After centrifugation, the top 8 ml from each LSM preparation was removed and discarded. The remaining lymphocyte-rich fluid was withdrawn to within approximately one-fourth inch above the erythrocyte pellet. These cells were washed three times in cold HBSS before resuspending in HBSS supplemented with 5% heat-inactivated SRBC-absorbed calf serum, 100 µg/ml penicillin, and 100 µg/ml streptomycin at 10^7, 10^6, and 10^5 viable, nucleated cells/ml.

j. Additional guidelines

(1) All cell preparations were stored on ice or refrigerated when not in use.
(2) All media were stored cold.
(3) Media were not allowed to turn basic. Bottles were tightly capped.
(4) All washes were centrifuged for 10 minutes at 1,000 rpm.

5. IgG plaque assay

a. SRBC were washed as described in the immunization procedure.
b. Base pours were warmed at 37° C in a 5% carbon dioxide atmosphere, and agarose tubes were held at 47° ± 2° C.
c. Pouring plaques: 0.1 ml 10% SRBC, 0.1 ml appropriate cell suspension dilution, and 0.2 ml of anti-mouse IgG (1:800 dilution) were added to cooled triplicate agarose tubes. The mixture was gently swirled and poured onto separate base pours. Plates were allowed to stand undisturbed at room temperature for 5 minutes. A similar set of triplicate plates was poured for each cell dilution, deleting only the anti-mouse IgG. These represent the IgM plaques.
d. All plates were incubated for 2 hours in a humidified incubator with 5% ± 0.5% carbon dioxide at 37° ± 0.5° C.
e. SRBC-absorbed complement was thawed, and a 1:10 dilution was made with HBSS (diluted 1:10) and kept on ice.
f. After the 2-hour incubation, 1.0 ml of the 1:10 complement dilution was added to each plate and plates were incubated an additional 75 minutes as above.
g. The complement was decanted from each plate, and the plates were refrigerated overnight. Plaques were counted with a high-intensity lamp.
h. For each assay, the following controls were performed in triplicate:

10% SRBC alone
10% SRBC plus complement
10% SRBC plus anti-mouse IgG
10% SRBC plus anti-mouse IgG plus complement

APPENDIX I

RESULTS OF SIX-MONTH SUPPLEMENTAL FEED STUDIES OF PENTACHLOROPHENOL

TABLE I1. LIVER MICROSOMAL ARYL HYDROCARBON HYDROXYLASE AND P450 LEVELS IN MALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Aryl Hydrocarbon Hydroxylase (b)	P450 (c)
Control + 3,4-Benzo[*a*]pyrene		
	1.60 ± 0.229	0.37 ± 0.016
Pure Pentachlorophenol		
0	0.30 ± 0.104	0.38 ± 0.094
200	0.46 ± 0.121	0.41 ± 0.050
500	0.84 ± 0.261	0.55 ± 0.040
1,500	(d) 1.41 ± 0.193	(e) 0.64 ± 0.080
Dowicide EC-7		
0	0.30 ± 0.104	0.38 ± 0.094
200	0.65 ± 0.393	0.47 ± 0.076
600	0.87 ± 0.303	0.52 ± 0.051
1,200	(e) 1.27 ± 0.334	(e) 0.66 ± 0.039
DP-2		
0	0.30 ± 0.104	0.38 ± 0.094
200	(e) 1.22 ± 0.208	(e) 0.68 ± 0.042
600	(d) 8.13 ± 1.168	(e) 0.84 ± 0.113
1,200	(d) 8.08 ± 1.936	(e) 1.02 ± 0.051
Technical-Grade Pentachlorophenol		
0	0.30 ± 0.104	0.38 ± 0.094
200	(e) 9.37 ± 1.322	(e) 0.96 ± 0.085
600	(e) 11.72 ± 1.768	(e) 0.89 ± 0.192

(a) Mean ± standard error; four animals were examined for each dose group; P values vs. the common control group used for the four studies.
(b) Units per milligrams protein
(c) Nanomoles per milligrams protein
(d) $P<0.01$
(e) $P<0.05$

TABLE I2. ANALYSIS OF NECROPSY BODY WEIGHT AND ORGAN WEIGHTS FOR MALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Weighed	Body Weight (gram)	Liver		Spleen		Thymus	
			Number Weighed	Weight (mg)	Number Weighed	Weight (mg)	Number Weighed	Weight (mg)
Pure Pentachlorophenol								
0	10	35.8 ± 0.85	10	1,933 ± 121	10	74 ± 5	10	30 ± 2
200	8	36.3 ± 0.80	8	(b) 2,228 ± 68	8	82 ± 4	8	27 ± 3
500	10	36.8 ± 0.79	10	(c) 2,359 ± 85	10	(c) 100 ± 6	10	31 ± 5
1,500	10	33.4 ± 0.54	10	(c) 3,106 ± 111	10	(c) 96 ± 5	9	27 ± 2
Dowicide EC-7								
0	10	35.8 ± 0.85	10	1,933 ± 121	10	74 ± 5	10	30 ± 2
200	9	37.8 ± 1.28	9	2,124 ± 109	9	(c) 101 ± 7	8	35 ± 3
600	10	35.4 ± 0.85	10	2,244 ± 101	10	(c) 111 ± 8	10	32 ± 3
1,200	10	(b) 32.1 ± 0.59	10	(c) 2,606 ± 119	10	(c) 94 ± 6	10	34 ± 4
DP-2								
0	10	35.8 ± 0.85	10	1,933 ± 121	10	74 ± 5	10	30 ± 2
200	10	(b) 39.3 ± 0.84	10	2,205 ± 107	10	85 ± 4	10	40 ± 3
600	10	35.2 ± 0.42	10	(c) 2,894 ± 68	10	(c) 126 ± 11	10	27 ± 3
1,200	8	35.1 ± 0.55	8	(c) 3,740 ± 161	8	(c) 113 ± 11	8	26 ± 3
Technical-Grade Pentachlorophenol								
0	10	35.8 ± 0.85	10	1,933 ± 121	10	74 ± 5	10	30 ± 2
200	10	38.0 ± 0.73	10	(b) 2,270 ± 67	10	87 ± 5	10	39 ± 4
600	10	37.5 ± 1.09	10	(c) 3,126 ± 102	10	(c) 103 ± 5	8	25 ± 3

(a) Mean ± standard error; early death or inadequate measurement is indicated if the number of animals in a group is less than 10; P values vs. the common control group used for the four studies.
(b) $P<0.05$
(c) $P<0.01$

TABLE I3. ANALYSIS OF NECROPSY BODY WEIGHT AND ORGAN WEIGHTS FOR FEMALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Weighed	Body Weight (gram)	Liver		Spleen		Thymus	
			Number Weighed	Weight (mg)	Number Weighed	Weight (mg)	Number Weighed	Weight (mg)
Pure Pentachlorophenol								
0	10	30.1 ± 0.86	10	1,376 ± 32	10	110 ± 6	10	46 ± 4
200	10	31.0 ± 0.89	10	(b) 1,591 ± 45	10	133 ± 10	10	53 ± 7
500	10	29.6 ± 0.70	10	(b) 1,570 ± 49	9	122 ± 9	10	41 ± 3
1,500	9	(c) 26.9 ± 0.56	9	(b) 1,911 ± 85	9	109 ± 5	9	36 ± 3
Dowicide EC-7								
0	10	30.1 ± 0.86	10	1,376 ± 32	10	110 ± 6	10	46 ± 4
200	9	31.0 ± 0.90	9	(b) 1,700 ± 63	9	115 ± 7	9	39 ± 5
600	10	29.6 ± 0.65	10	(b) 1,754 ± 44	10	108 ± 6	10	47 ± 6
1,200	10	(c) 27.4 ± 0.50	10	(b) 1,929 ± 80	10	(c) 92 ± 4	10	43 ± 3
DP-2								
0	10	30.1 ± 0.86	10	1,376 ± 32	10	110 ± 6	10	46 ± 4
200	10	33.6 ± 0.73	10	(b) 1,763 ± 47	10	107 ± 6	10	47 ± 4
600	10	31.2 ± 0.53	10	(b) 1,963 ± 39	10	(c) 93 ± 4	10	46 ± 4
1,200	9	28.1 ± 0.92	9	(b) 2,440 ± 84	9	(b) 84 ± 3	9	39 ± 3
Technical-Grade Pentachlorophenol								
0	10	30.1 ± 0.86	10	1,376 ± 32	10	110 ± 6	9	46 ± 4
200	10	30.7 ± 1.11	10	(b) 1,638 ± 50	10	109 ± 9	9	40 ± 4
600	10	30.3 ± 0.62	10	(b) 2,396 ± 47	10	(c) 94 ± 4	9	42 ± 2

(a) Mean ± standard error; early death or inadequate measurement is indicated if the number of animals in a group is less than 10; P values vs. the common control group used for the four studies.
(b) $P<0.01$
(c) $P<0.05$

TABLE I4. ANALYSIS OF ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Weighed	Liver Weight/ Body Weight	Number Weighed	Spleen Weight/ Body Weight	Number Weighed	Thymus Weight/ Body Weight
Pure Pentachlorophenol						
0	10	5.4 ± 0.29	10	2.1 ± 0.17	10	8.4 ± 0.51
200	8	6.2 ± 0.24	8	2.3 ± 0.09	8	7.4 ± 0.70
500	10	(b) 6.4 ± 0.20	10	(c) 2.7 ± 0.19	10	8.3 ± 1.33
1,500	10	(b) 9.3 ± 0.29	10	(b) 2.9 ± 0.12	9	8.2 ± 0.56
Dowicide EC-7						
0	10	5.4 ± 0.29	10	2.1 ± 0.17	10	8.4 ± 0.51
200	9	5.6 ± 0.21	9	(c) 2.7 ± 0.19	8	9.1 ± 0.49
600	10	(c) 6.3 ± 0.25	10	(b) 3.1 ± 0.21	10	9.2 ± 0.90
1,200	10	(b) 8.1 ± 0.26	10	(b) 2.9 ± 0.15	10	10.6 ± 1.21
DP-2						
0	10	5.4 ± 0.29	10	2.1 ± 0.17	10	8.4 ± 0.51
200	10	5.6 ± 0.22	10	2.2 ± 0.09	10	10.2 ± 0.8
600	10	(b) 8.2 ± 0.22	10	(b) 3.6 ± 0.33	10	7.7 ± 0.80
1,200	8	(b) 10.6 ± 0.38	8	(b) 3.2 ± 0.28	8	7.5 ± 0.94
Technical-Grade Pentachlorophenol						
0	10	5.4 ± 0.29	10	2.1 ± 0.17	10	8.4 ± 0.51
200	10	(c) 6.0 ± 0.15	10	2.3 ± 0.12	10	10.1 ± 0.97
600	10	(b) 8.3 ± 0.13	10	(b) 2.8 ± 0.12	8	6.7 ± 0.53

(a) Mean in milligrams per gram ± standard error; ratios multiplied by 10; number = number of animals with both organ and body weights measured at necropsy; P values vs. the common control group used for the four studies.
(b) $P<0.01$
(c) $P<0.05$

TABLE I5. ANALYSIS OF ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR FEMALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Weighed	Liver Weight/ Body Weight	Number Weighed	Spleen Weight/ Body Weight	Number Weighed	Thymus Weight/ Body Weight
Pure Pentachlorophenol						
0	10	4.6 ± 0.12	10	3.7 ± 0.23	9	1.5 ± 0.13
200	10	(b) 5.2 ± 0.19	10	4.4 ± 0.52	10	1.7 ± 0.20
500	10	(c) 5.3 ± 0.09	9	4.1 ± 0.26	10	1.4 ± 0.11
1,500	9	(c) 7.1 ± 0.20	9	4.1 ± 0.22	9	1.3 ± 0.10
Dowicide EC-7						
0	10	4.6 ± 0.12	10	3.7 ± 0.23	9	1.5 ± 0.13
200	9	(c) 5.5 ± 0.08	9	3.7 ± 0.16	9	1.3 ± 0.16
600	10	(c) 5.9 ± 0.17	10	3.7 ± 0.23	10	1.6 ± 0.18
1,200	10	(c) 7.1 ± 0.30	10	3.4 ± 0.15	10	1.6 ± 0.09
DP-2						
0	10	4.6 ± 0.12	10	3.7 ± 0.23	9	1.5 ± 0.13
200	10	(c) 5.3 ± 0.15	10	3.2 ± 0.19	10	1.4 ± 0.11
600	10	(c) 6.3 ± 0.11	10	(b) 3.0 ± 0.14	10	1.5 ± 0.13
1,200	9	(c) 8.5 ± 0.18	9	(b) 2.9 ± 0.09	9	1.3 ± 0.09
Technical-Grade Pentachlorophenol						
0	10	4.6 ± 0.18	10	3.7 ± 0.23	9	1.5 ± 0.13
200	10	(c) 5.4 ± 0.14	10	3.6 ± 0.37	9	1.3 ± 0.12
600	10	(c) 7.9 ± 0.11	10	3.1 ± 0.14	9	1.4 ± 0.06

(a) Mean in milligrams per gram ± standard error; ratios multiplied by 10; number = number of animals with both organ and body weights measured at necropsy; P values vs. the common control group used for the four studies.
(b) $P<0.05$
(c) $P<0.01$

TABLE I6. ANALYSIS OF TOTAL LIVER PORPHYRINS AND URINARY PORPHYRIN LEVELS FOR MALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Liver Porphyrins Number Examined	Liver Porphyrins nmol/g	Urinary Coproporphyrins Number Examined	Urinary Coproporphyrins nmol/ml	Urinary Uroporphyrins Number Examined	Urinary Uroporphyrins nmol/ml
Pure Pentachlorophenol						
0	10	0.31 ± 0.009	2	0.09 ± 0.067	2	0.00 ± 0.000
200	8	0.32 ± 0.013	2	0.12 ± 0.109	2	0.00 ± 0.000
500	10	0.30 ± 0.010	2	0.01 ± 0.012	2	0.00 ± 0.001
1,500	10	(b) 0.40 ± 0.026	2	0.09 ± 0.001	2	(c) 0.03 ± 0.006
Dowicide EC-7						
0	10	0.31 ± 0.009	2	0.09 ± 0.067	2	0.00 ± 0.000
200	9	(c) 0.28 ± 0.011	2	0.00 ± 0.001	2	0.01 ± 0.005
600	10	0.30 ± 0.012	2	0.03 ± 0.004	2	0.01 ± 0.004
1,200	10	0.30 ± 0.009	2	0.03 ± 0.009	2	0.01 ± 0.009
DP-2						
0	10	0.31 ± 0.009	2	0.09 ± 0.067	2	0.00 ± 0.000
200	10	0.27 ± 0.015	2	0.03 ± 0.008	2	0.02 ± 0.007
600	10	0.28 ± 0.008	2	0.03 ± 0.013	2	0.06 ± 0.041
1,200	8	0.33 ± 0.022	2	0.02 ± 0.015	2	(c) 0.10 ± 0.008
Technical-Grade Pentachlorophenol						
0	10	0.31 ± 0.009	2	0.09 ± 0.067	2	0.00 ± 0.000
200	10	(b) 0.57 ± 0.028	2	0.03 ± 0.009	2	0.00 ± 0.002
600	10	(b) 0.52 ± 0.013	2	0.03 ± 0.007	2	0.03 ± 0.025

(a) Mean ± standard error; for the urinary porphyrin studies, the data are for the mean of two measurements for each cage of five animals; P values vs. the common control group used for the four studies.
(b) $P<0.01$
(c) $P<0.05$

TABLE I7. ANALYSIS OF TOTAL LIVER PORPHYRINS AND URINARY PORPHYRIN LEVELS FOR FEMALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Liver Porphyrins Number Examined	ng/g	Urinary Coproporphyrins Number Examined	µg/24 h	Urinary Uroporphyrins Number Examined	µg/24 h
Pure Pentachlorophenol						
0	10	0.20 ± 0.006	2	0.44 ± 0.084	2	0.003 ± 0.003
200	10	0.19 ± 0.004	2	0.56 ± 0.120	2	0.02 ± 0.013
500	10	0.19 ± 0.010	2	1.20 ± 0.628	2	0.04 ± 0.002
1,500	9	(b) 0.17 ± 0.006	2	(c) 2.39 ± 0.350	2	(c) 0.09 ± 0.003
Dowicide EC-7						
0	10	0.20 ± 0.006	2	0.44 ± 0.084	2	0.003 ± 0.003
200	9	(b) 0.43 ± 0.019	2	1.03 ± 0.161	2	0.04 ± 0.000
600	10	(b) 0.39 ± 0.013	2	0.92 ± 0.062	2	0.02 ± 0.002
1,200	10	(b) 0.43 ± 0.016	2	0.67 ± 0.135	2	0.01 ± 0.007
DP-2						
0	10	0.20 ± 0.006	2	0.44 ± 0.084	2	0.003 ± 0.003
200	10	(b) 0.35 ± 0.019	2	0.44 ± 0.096	2	0.00 ± 0.000
600	10	(b) 0.43 ± 0.031	2	1.28 ± 0.119	2	0.06 ± 0.008
1,200	10	(b) 0.44 ± 0.033	2	1.57 ± 0.382	2	(c) 0.08 ± 0.002
Technical-Grade Pentachlorophenol						
0	10	0.20 ± 0.006	2	0.44 ± 0.084	2	0.003 ± 0.003
200	10	0.22 ± 0.008	2	1.05 ± 0.255	2	(d) 0.077 ± 0.023
600	10	(b) 0.73 ± 0.026	2	(c) 1.49 ± 0.070	2	(d) 0.073 ± 0.008

(a) Mean ± standard error; for the urinary porphyrin studies, the data are for the mean of two measurements for each cage of five animals; P values vs. the common control group used for the four studies.
(b) $P<0.01$
(c) $P<0.05$
(d) $P<0.01$ by Dunnett's test (Dunnett, 1955); due to the small number of observations, the dosed groups were not significantly different from the controls by Dunn's (Dunn, 1964) or Shirley's (Shirley, 1977) test.

TABLE I8. CLINICAL CHEMICAL ANALYSES FOR MALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Examined	SGPT (b)	Number Examined	SGOT (c)	Number Examined	γ-GTP (d)
Pure Pentachlorophenol						
0	9	40.7 ± 6.83	9	166 ± 34.2	9	0.00 ± 0.000
200	8	(e) 63.9 ± 8.07	8	133 ± 13.4	8	0.13 ± 0.125
500	10	(e) 122.4 ± 20.24	10	204 ± 61.9	10	0.10 ± 0.061
1,500	10	(e) 443.2 ± 89.78	10	216 ± 31.4	10	(e) 2.76 ± 1.037
Dowicide EC-7						
0	9	40.7 ± 6.83	9	166 ± 34.2	9	0.00 ± 0.000
200	9	42.1 ± 3.19	9	(e) 64 ± 7.4	9	0.00 ± 0.000
600	9	(e) 66.8 ± 12.09	9	111 ± 15.4	9	0.39 ± 0.389
1,200	10	(e) 143 ± 47.67	10	216 ± 62.3	10	0.00 ± 0.000
DP-2						
0	9	40.7 ± 6.8	9	165.89 ± 34.2	9	0.00 ± 0.000
200	10	94.2 ± 47.0	10	205.10 ± 50.9	10	0.21 ± 0.149
600	10	(e) 233 ± 73.9	10	189.10 ± 34.3	10	(f) 0.44 ± 0.327
1,200	8	(e) 2,031 ± 958	8	(e) 1,488 ± 647	8	(e) 9.11 ± 4.708
Technical-Grade Pentachlorophenol						
0	9	40.7 ± 6.83	9	166 ± 34.2	9	0.00 ± 0.000
200	10	(e) 223 ± 29	10	176 ± 21.2	10	0.00 ± 0.000
600	10	(e) 392 ± 40	10	(e) 267 ± 19.8	10	0.26 ± 0.260

(a) Mean ± standard error; P values vs. the common control group used for the four studies.
(b) SGPT = serum glutamic-pyruvic transaminase activity; international units per liter
(c) SGOT = serum glutamic-oxaloacetic transaminase activity; international units per liter
(d) γ-GTP = γ-glutamyl transpeptidase activity; international units per liter
(e) $P<0.01$
(f) $P<0.05$

TABLE I9. CLINICAL CHEMICAL ANALYSES FOR FEMALE MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Examined	SGPT (b)	Number Examined	SGOT (c)
Pure Pentachlorophenol				
0	10	17.8 ± 1.23	10	92.5 ± 11.61
200	10	(d) 19.1 ± 1.68	10	82.6 ± 12.16
500	10	(d) 37.9 ± 7.05	10	189 ± 80.6
1,500	9	(d) 250 ± 35.5	9	(d) 278 ± 31.8
Dowicide EC-7				
0	10	17.8 ± 1.23	10	92.5 ± 11.61
200	9	(d) 31.3 ± 2.19	9	104 ± 14.0
600	10	(d) 37.8 ± 3.03	10	99.4 ± 8.30
1,200	9	(d) 53.4 ± 4.04	10	137 ± 30.8
DP-2				
0	10	17.8 ± 1.23	10	92.5 ± 11.61
200	9	(e) 25.3 ± 2.83	9	107 ± 22.2
600	10	(d) 83.5 ± 15.21	10	121 ± 20.5
1,200	10	(d) 396 ± 41.0	10	(d) 363 ± 32.2
Technical-Grade Pentachlorophenol				
0	10	17.8 ± 1.23	10	92.5 ± 11.61
200	10	(d) 69.6 ± 11.29	10	154 ± 31.6
600	10	(d) 126 ± 11.8	10	(d) 166 ± 11.2

(a) Mean ± standard error; P values vs. the common control group used for the four studies.
(b) SGPT = serum glutamic-pyruvic transaminase activity; international units per liter
(c) SGOT = serum glutamic-oxaloacetic transaminase activity; international units per liter
(d) $P<0.01$
(e) $P<0.05$

TABLE I10. EFFECTS OF PENTACHLOROPHENOL ON ANTIBODY RESPONSE OF MALE MICE TO SHEEP ERYTHROCYTES IN THE SIX-MONTH FEED STUDIES

Concentration (ppm)	IgG Plaque-Forming Cells/ 10^6 Spleen Cells (b)	Hemagglutination Titers (a)	
		Total Immunoglobulins (IgM, IgG, IgA) (c)	2-Mercaptoethanol-Resistant Immunoglobulins (IgG, IgA) (c)
(d) 0	64	40	4
Pure Pentachlorophenol			
0	181 ± 22	88 ± 19 (10)	19 ± 6 (10)
200	195 ± 20	148 ± 50 (5)	20 ± 6 (5)
500	166 ± 43	144 ± 16 (5)	19 ± 5 (5)
1,500	140 ± 25	72 ± 27 (5)	14 ± 5 (5)
Dowicide EC 7			
0	268 ± 28	145 ± 43 (8)	28 ± 7 (8)
200	247 ± 71	107 ± 27 (3)	13 ± 3 (3)
600	212 ± 28	53 ± 27 (3)	13 ± 3 (3)
1,200	291 ± 74	120 ± 40 (3)	32 ± 16 (3)
DP 2			
0	268 ± 28	145 ± 43 (8)	28 ± 7 (8)
200	147 ± 39	80 ± 0 (2)	40 ± 24 (2)
600	117 ± 31	50 ± 10 (4)	12 ± 2 (4)
1,200	41 ± 13	93 ± 35 (3)	93 ± 81 (3)
Technical Grade Pentachlorophenol			
0	181 ± 22	88 ± 19 (10)	19 ± 6 (10)
200	78 ± 25	110 ± 30 (4)	13 ± 3 (4)
600	20 ± 4	64 ± 27 (5)	8 ± 2 (5)

(a) Reciprocal of last dilution of test serum giving a positive hemagglutination reaction
(b) Individual animal data could not be obtained for statistical analyses; means and standard errors are taken from the laboratory report
(c) Mean ± standard error (number of observations)
(d) Sentinel control mice were injected intraperitoneally with 2 5 mg of hydrocortisone acetate 48 h before testing The cells were pooled, and thus statistical significance could not be determined

TABLE I11. MEAN BODY TEMPERATURES FOR MICE IN THE SIX-MONTH FEED STUDIES OF PENTACHLOROPHENOL (a)

Concentration (ppm)	Number Examined (b)	Male		Female	
		Week 9	Week 26	Week 9	Week 26
0	10	35.1 ± 0.6	35.8 ± 0.7	36.1 ± 0.7	36.8 ± 0.9
Pure Pentachlorophenol					
200	10	35.4 ± 0.5	(c) 34.9 ± 0.4	36.3 ± 0.5	36.3 ± 0.6
500	10	35.3 ± 0.9	35.7 ± 0.5	36.1 ± 0.5	36.1 ± 0.5
1,500	10	35.5 ± 0.9	35.6 ± 0.4	36.4 ± 0.6	36.0 ± 0.4
Dowicide EC-7					
200	10	35.1 ± 0.9	(d) 35.5 ± 0.4	36.6 ± 0.6	36.2 ± 0.4
600	10	35.2 ± 1.0	35.7 ± 0.8	36.6 ± 0.7	36.4 ± 0.7
1,200	10	35.5 ± 0.9	35.3 ± 0.7	36.8 ± 0.5	36.1 ± 0.5
DP-2					
200	10	35.2 ± 0.3	35.2 ± 0.5	36.4 ± 0.5	36.4 ± 0.6
600	10	35.6 ± 1.0	36.0 ± 0.8	36.2 ± 0.4	36.7 ± 0.8
1,200	10	35.4 ± 0.3	(d) 35.4 ± 0.8	36.9 ± 0.7	36.8 ± 0.6
Technical-Grade Pentachlorophenol					
200	10	35.0 ± 0.9	35.4 ± 0.8	36.4 ± 0.7	35.3 ± 0.8
600	10	34.7 ± 0.6	34.9 ± 0.8	36.4 ± 0.4	36.2 ± 0.7
1,800	10	35.5 ± 0.8	(e)	36.3 ± 0.5	(f) 35.6 ± 0.3

(a) Mean ± standard deviation; rectal temperature reported in degrees Celsius; common control groups used for all four grades of pentachlorophenol.
(b) Except as noted
(c) Eight examined
(d) Nine examined
(e) No data are reported due to 100% mortality of the group.
(f) Three examined

APPENDIX J

AUDIT SUMMARY

APPENDIX J. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and the preliminary draft (June 1987) of NTP Technical Report No. 349 for the 2-year studies in mice of technical-grade pentachlorophenol and pentachlorophenol, Dowicide EC-7, were audited for the NIEHS at the NTP Archives during February, March, and July 1987 by Dynamac Corporation. Complete reports are on file at the NIEHS. The audit included a review of the following:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records, including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning disposition codes, condition codes, tissue accountability, correlation of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microsopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of mice in all study groups, plus other relevant cases to verify animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group to examine for proper match and inventory.
(8) All red-lined diagnoses on the intermediate pathology tables to verify incorporation of changes in the final tables.
(9) Correlation between the data, results, and procedures for the 2-year studies presented in the preliminary draft of the Technical Report and the records available at the NTP Archives.

Inlife procedures and events were documented adequately by the archival records, with a few exceptions. For example, the records did not document the disposition of surplus animals; twice daily cage checks; feeder, cage, and rack changes; and light cycle checks. Original feed consumption data were absent for two measurement dates, and animal room environmental condition records were not recorded for 35/730 study days. These gaps in study documentation were generally covered by information provided in laboratory reports or assessed during the audit using ancillary information, such as general animal health, and determined to be of no significance. The hematology and clinical pathology data were not included as part of the audit.

Formulated diets were prepared properly over the course of the studies, and administration to animals was documented by monthly feed consumption measurement records. Feed lots more than 90 days postmilling were used on 37/104 mixing dates. Random samples of group mean body weight and feed consumption measurements were recalculated and found to be accurate. Of the external masses noted among the inlife records, 57/59 in the technical-grade pentachlorophenol mice and 53/53 in the Dowicide EC-7 mice were correlated with necropsy observations.

For the technical-grade pentachlorophenol study, an audit of the pathology specimens showed that individual animal identifiers (clipped toes and punched ears) were present and correct in the tissue bags for 54/62 mice examined; identifiers were missing or mutilated in 6 mice, whereas the toes of 2 others were either clipped incorrectly or mutilated. This, along with the correspondence of other study records, indicated that individual animal identity was maintained throughout the studies. The audit found 7 untrimmed potential lesions (none in target organs) among the 62 animals examined The residual intestinal segments for 31/62 animals were incompletely opened, and two potential lesions were evident by external examination. Although the heart and stomach of low dose mice were not required to be examined microscopically, it was noted that they were inconsistently opened at necropsy.

All blocks and slides were present and labeled correctly, and they matched each other properly. The correlation between gross and microscopic observations was good, and all diagnoses indicated on red-lined intermediate tables had been incorporated into the final pathology tables.

For the Dowicide EC-7 study, the pathology audit findings were similar and only specific findings follow. Individual animal identifiers were present and correct in the tissue bags for 79/91 mice examined. The toes for two mice were clipped incorrectly, but ears indicated that the animals were in the correct dose group. The identifiers for the remaining 10 mice were either not present, mutilated, or unreadable. Comparison of the evidence of lesions present in the residual tissues for two low dose male mice with the gross observations recorded on their necropsy record forms indicated that the bags had been cross-labeled, but there was no evidence that animals in the study had been mixed up before necropsy or between groups. The audit identified 19 untrimmed potential lesions (4 in liver); the residual intestinal segments were incompletely opened in 42/91 animals, and 1 potential lesion was evident by external examination. Tissue accountability was generally good but was lower than usual in the low and mid dose groups where complete histopathology was not required (e.g., spleen approximately 41% and nasal cavity approximately 24%).

Full details about these and other audit findings are presented in audit reports that are on file at the NIEHS were reviewed by NTP staff when the study interpretations were prepared. In conclusion, the data and results presented in the preliminary draft of the Technical Report for the 2-year feed studies of pentachlorophenol are supported by the records at the NTP Archives.

* U. S. GOVERNMENT PRINTING OFFICE:1989-241-221:80398