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TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2,4-DICHLOROPHENOL

(CAS NO. 120-83-2)

IN F344/N RATS AND 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 2,4-DICHLOROPHENOL

(CAS NO. 120-83-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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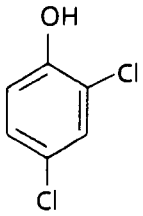

2,4-DICHLOROPHENOL

CAS No. 120-83-2

$C_6H_4Cl_2O$ Molecular weight 163.0

Synonyms: 2,4-DCP; 2,4-dichlorohydroxybenzene

ABSTRACT

2,4-Dichlorophenol is a chemical intermediate used principally in the manufacture of the herbicide 2,4-dichlorophenoxyacetic acid. Toxicology and carcinogenesis studies were conducted by feeding diets containing 2,4-dichlorophenol (greater than 99% pure) for 14 days, 13 weeks, or 2 years to groups of F344/N rats and B6C3F$_1$ mice of each sex. Genetic toxicology tests were conducted in *Salmonella typhimurium*, mouse L5178Y lymphoma cells, and Chinese hamster ovary (CHO) cells.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, male and female rats and mice were given diets containing 2,4-dichlorophenol at concentrations up to 40,000 ppm. One high dose male mouse died before the end of the studies; no deaths occurred in any other group, and no compound-related lesions were seen at necropsy in rats or mice. In the 13-week studies, groups of 10 rats and 10 mice of each sex were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm 2,4-dichlorophenol. All rats lived to the end of the studies, whereas all mice that received 40,000 ppm died during the first 3 weeks of the studies. Final mean body weights of rats that received 20,000 or 40,000 ppm and of male mice that received 20,000 ppm were at least 10% lower than those of controls. Bone marrow atrophy in rats and necrosis and syncytial alteration (multinucleated hepatocytes) in the liver of male mice were compound-related effects. Two-year studies were conducted by feeding diets containing 0, 5,000, or 10,000 ppm 2,4-dichlorophenol to groups of 50 male rats and 50 male and 50 female mice for 103 weeks. Groups of 50 female rats received diets containing 0, 2,500, or 5,000 ppm.

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose male and female rats, high dose male mice, and both dosed groups of female mice were generally lower than those of controls. No significant differences in survival were observed between any groups of rats or mice of either sex (male rats: control, 33/50; low dose, 25/50; high dose, 32/50; female rats: 34/50; 43/50; 40/50; male mice: 33/50; 32/50; 31/50; female mice: 45/50; 40/50; 43/50). The average daily feed consumption by rats in the low dose and high dose groups was 94%-97% that by the controls. The estimated daily mean consumption of 2,4-dichlorophenol was 210 or 440 mg/kg for low dose or high dose male rats and 120 or 250 mg/kg for low dose or high dose female rats. The average daily feed consumption by mice in the low dose and high dose groups was 97% and 78% of that by the controls for males and 94% and 85% for females. The estimated daily mean consumption of 2,4-dichlorophenol was 800 or 1,300 mg/kg for low dose or high dose male mice and 430 or 820 mg/kg for low dose or high dose female mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: There were no compound-related increased incidences of neoplastic lesions in rats or mice. The incidence of mononuclear cell leukemia

was decreased in dosed male rats relative to that in controls (control, 31/50; low dose, 17/50; high dose, 17/50); the incidence of malignant lymphomas was decreased in high dose female mice (4/50) relative to that in controls (12/50). Syncytial alteration of hepatocytes was observed at increased incidences in dosed male mice (11/50; 33/49; 42/48).

Genetic Toxicology: The mutagenic effect of 2,4-dichlorophenol in *S. typhimurium* strain TA1535 was considered to be equivocal only in the presence of hamster S9; 2,4-dichlorophenol produced no increases in revertant colonies in strains TA98, TA100, or TA1537 with or without exogenous metabolic activation. 2,4-Dichlorophenol increased trifluorothymidine (Tft) resistance in the mouse L5178Y assay without metabolic activation; it was not tested with activation. In cultured CHO cells, 2,4-dichlorophenol did not induce chromosomal aberrations but did significantly increase the frequency of sister chromatid exchanges (SCEs) both in the presence and absence of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of 2,4-dichlorophenol 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 *no evidence of carcinogenic activity** for male F344/N rats fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol or for female F344/N rats fed diets containing 2,500 or 5,000 ppm 2,4-dichlorophenol. There was *no evidence of carcinogenic activity* for male or female B6C3F$_1$ mice fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol.

SUMMARY OF THE TWO-YEAR AND GENETIC TOXICOLOGY STUDIES OF 2,4-DICHLOROPHENOL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
0, 5,000, or 10,000 ppm 2,4-dichlorophenol	0, 2,500, or 5,000 ppm 2,4-dichlorophenol	0, 5,000, or 10,000 ppm 2,4-dichlorophenol	0, 5,000, or 10,000 ppm 2,4-dichlorophenol
Body weights in the 2-year study			
Lower in high dose group	Lower in high dose group	Lower in high dose group	Lower in dosed groups
Survival rates in the 2-year study			
33/50; 25/50; 32/50	34/50; 43/50; 40/50	33/50; 32/50; 31/50	45/50; 40/50; 43/50
Nonneoplastic effects			
None	None	Syncytial alteration of hepatocytes	None
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence
Genetic toxicology			
S. typhimurium (gene mutation)	Mouse L5178Y/TK$^{+/-}$ (Tft resistance)	CHO cells in vitro: SCE	CHO cells in vitro: Aberration
Negative without S9; equivocal with S9	Positive without S9; not tested with S9	Positive with and without S9	Negative with and without S9

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that 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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,4-Dichlorophenol is based on the 13-week studies that began in April 1980 and ended in July 1980 and on the 2-year studies that began in February 1981 and ended in March 1983 at Battelle Columbus Laboratories (Columbus, Ohio).

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The members of the Peer Review Panel who evaluated the draft Technical Report on 2,4-dichlorophenol 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.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2,4-DICHLOROPHENOL

On April 18, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of 2,4-dichlorophenol received peer 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 (NIEHS), Research Triangle Park, North Carolina.

Dr. R.L. Melnick, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats or for male or female mice).

Dr. Lijinsky, a principal reviewer, agreed with the conclusions. He asked for the rationale for selecting a top dose for male rats which was double that for female rats. Dr. Melnick said that the selection of 5,000 ppm as the high dose for female rats was based on the observation of bone marrow atrophy in 6/10 female rats given 10,000 ppm in the 13-week study.

Dr. Perera, the second principal reviewer, agreed with the conclusions. She suggested that the chemical might have been evaluated better in an initiation-promotion assay, as it had been shown to be positive as a promoter in a mouse skin model.

Dr. Gallo, the third principal reviewer, agreed with the conclusions. He questioned why drinking water was not the route of administration because the presence of 2,4-dichlorophenol in drinking water was one rationale for conducting the studies. Dr. Melnick replied that the limited water solubility of 2,4-dichlorophenol would have reduced the top dose to less than half that used in the feed studies.

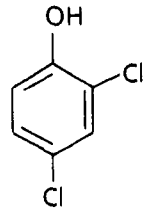
There was some discussion about the positive trend for forestomach tumors in male mice and why this finding was not given more weight. Dr. J. Huff, NIEHS, explained that the lack of an increased incidence in hyperplasia in male and female mice, together with the negative trend for these lesions in female mice, suggested that the forestomach tumors were not chemically related.

Dr. Lijinsky moved that the Technical Report on 2,4-dichlorophenol be accepted with minor revisions and with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Perera seconded the motion, which was approved unanimously with 10 votes.

I. INTRODUCTION

Physical and Chemical Properties, Use, Production, and Exposure
Metabolism and Pharmacokinetics
Animal Toxicity
Developmental Toxicity
Carcinogenicity
Genetic Toxicology
Human Effects
Study Rationale

I. INTRODUCTION



2,4-DICHLOROPHENOL

CAS No. 120-83-2

$C_6H_4Cl_2O$ Molecular weight 163.0

Synonyms: 2,4-DCP; 2,4-dichlorohydroxybenzene

Physical and Chemical Properties, Use, Production, and Exposure

2,4-Dichlorophenol is a colorless, crystalline solid (melting point: 45° C; boiling point: 210° C at 760 mm mercury; vapor pressure: 1.0 mm mercury at 53.0° C) which is slightly soluble in water at neutral pH (0.45% at 20° C) and very soluble in alcohol, ether, and benzene. 2,4-Dichlorophenol acts as a weak acid (pK_a = 7.85) and is highly soluble in alkaline solutions, readily forming the corresponding salt. 2,4-Dichlorophenol is synthesized by direct chlorination of phenol or by chlorination of monochlorophenol (Kirk-Othmer, 1979).

2,4-Dichlorophenol is used principally as a chemical intermediate in the manufacture of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). 2,4-Dichlorophenol has also been used in the manufacture of methylated chlorophenols used for mothproofing and in antiseptics and seed disinfectants. 2,4-Dichlorophenol can be reacted with benzene sulfonyl chloride to produce miticides or can be further chlorinated to pentachlorophenol, a wood preservative (USEPA, 1980). There is no commercial application for 2,4-dichlorophenol itself. The TSCA Initial Inventory indicated that the domestic production of 2,4-dichlorophenol was 22-120 million pounds in 1977 (USEPA, 1987).

Environmental contamination by 2,4-dichlorophenol may occur as a result of microbial degradation or photodecomposition of the herbicides 2,4-D or nitrofen (2,4-dichlorophenyl-*p*-nitrophenyl ether), from chlorination of drinking water and industrial and municipal waste waters by water disinfection plants, or from agricultural runoff or industrial waste discharges (Ahlborg and Thunberg, 1980; USEPA, 1980; Exon, 1984). Degradation of 2,4-D by soil *Arthrobacter sp.* has been shown to involve initial conversion to 2,4-dichlorophenol (Loos et al., 1967a,b). In soil, 2,4-dichlorophenol can undergo methylation to 2,4-dichloroanisole or degradation to carbon dioxide via ring fission (Smith, 1985). 2,4-Dichlorophenol was identified in seed, straw, and forage samples obtained from Proso millet treated with 2,4-D (Cook et al., 1983). 2,4-Dichlorophenol has been detected in drinking water supplies in the United States (Shackelford and Keith, 1976); the highest concentration reported was 36 µg/liter. Chlorophenols have been found in the effluent from a 2,4-D manufacturing plant at concentrations ranging from 68 to 125 mg/liter, with the 2,4-dichlorophenol content ranging as high as 89% of the total (USEPA, 1980). Because of its low vapor pressure and nonvolatility from alkaline solutions, removal of 2,4-dichlorophenol from surface water via volatilization is expected to be a very slow process (Fed. Regist., 1981). The Environmental Protection Agency water quality criterion level for 2,4-dichlorophenol is 3.09 mg/liter based on toxicologic data; however, for controlling undesirable taste and odor qualities of ambient water, the estimated level is 0.3 µg/liter (USEPA, 1980).

Metabolism and Pharmacokinetics

2,4-Dichlorophenol (0.1 mM) inhibited the activity of rat liver microsomal arylhydrocarbon hydroxylase and UDP-glucuronosyltransferase to about 60% of control levels (Ahotupa et al., 1981). It was suggested that inhibition of these enzymes could affect the in vivo biotransformation of other xenobiotics.

Chlorophenols are readily absorbed from the gastrointestinal tract and are excreted rapidly in urine as sulfonate or glucuronide conjugates (Exon, 1984).

The metabolism and distribution of 2,4-dichlorophenol were studied in male Sprague Dawley rats administered 10 mg/kg 2,4-dichlorophenol by intravenous injection (Somani and Khalique, 1982). 2,4-Dichlorophenol was rapidly metabolized to the glucuronide and other conjugates that were rapidly eliminated; conjugates of 2,4-dichlorophenol were detected in plasma within 10 minutes after administration of the compound; the half-lives of 2,4-dichlorophenol and its conjugates in plasma, liver, kidney, fat, and brain ranged from 4 to 30 minutes. The tissue/plasma concentration ratios of 2,4-dichlorophenol and its conjugates were higher in the kidney than in the liver, fat, or brain. Sixty minutes after intravenous administration, tissue/plasma concentration ratios for 2,4-dichlorophenol and total conjugates were 116.8 and 3.96 for the kidney, 30.0 and 0.38 for the liver, 5.75 and 0.02 for fat, and 0.25 and 0.00 for the brain. Residues of 2,4-dichlorophenol were found in the kidney and liver, but not in fat or muscle, of sheep and cattle fed diets containing up to 2,000 ppm of 2,4-D for 28 days (Clark et al., 1975). Thus, the kidney and liver appear to be the organs with the greatest affinity for 2,4-dichlorophenol and its conjugates. In rats dosed with [^{14}C]pentachlorophenol through drinking water for 4 weeks, the highest levels of radioactivity were also found in the liver and kidney (Ahlborg and Thunberg, 1980).

Somani et al. (1984) isolated two metabolites of 2,4-dichlorophenol in isolated perfused rat liver; these were tentatively identified as dichloromethoxyphenols. The principal metabolite of 2,4-dichlorophenol was the glucuronide conjugate of the parent compound.

Animal Toxicity

In rats, the acute LD_{50} of 2,4-dichlorophenol was 580 mg/kg after oral administration and 1,730 mg/kg after subcutaneous administration (Deichmann, 1943). Vernot et al. (1977) reported an acute oral LD_{50} of 2,830 mg/kg for 2,4-dichlorophenol in male Sprague Dawley rats and 1,630 mg/kg in male CF-1 mice. In another study, the acute oral LD_{50} of 2,4-dichlorophenol was reported to be 1,630 mg/kg in ICR mice and 3,670 and 4,500 mg/kg in male and female Sprague Dawley rats, respectively (Kobayashi et al., 1972). Similar acute oral LD_{50} values were reported by Borzelleca et al. (1985a) for 2,4-dichlorophenol in CD-1 mice (male: 1,276 mg/kg; female: 1,352 mg/kg). The LD_{50} in rats administered 2,4-dichlorophenol in olive oil by intraperitoneal injection was 430 mg/kg (Farquharson et al., 1958). Differences in the acute toxicity of 2,4-dichlorophenol may be due in part to the different vehicle solvents used. In general, LD_{50} values in mice are lower than those in rats.

Clinical signs of toxicity in rats administered fatal doses of chlorophenols include restlessness, increased rate of respiration, and motor weakness; tremors, clonic convulsions, dyspnea, and coma followed and continued until death (Deichmann, 1943). Clinical signs of intoxication by 2,4-dichlorophenol in mice include ataxia, loss of righting reflex, slight tremors, salivation, labored breathing, and depression (Borzelleca et al., 1985b).

Groups of male ICR mice were fed diets containing 0, 200, 500, 1,000, or 2,000 ppm 2,4-dichlorophenol for 6 months (Kobayashi et al., 1972). The estimated average intake of 2,4-dichlorophenol in the three highest dose groups was 45, 100, and 230 mg/kg per day, respectively. There were no compound-related changes in behavior, growth rate, serum glutamate-oxaloacetate transaminase activity, or serum glutamate-pyruvate transaminase activity. Minor histologic changes in the liver (infiltration of round cells and swelling of hepatocytes) were observed in the 230 mg/kg dose group.

Administration of 2,4-dichlorophenol in drinking water (containing 10% Emulphor) to CD-1 mice for 90 days at concentrations of 0.2, 0.6, or 2.0 mg/ml resulted in mean daily doses of 40, 114, or 383 mg/kg for males and 50, 143, or 491 mg/kg for females (Borzelleca et al., 1985b); no significant alterations in body weight, organ weights, or hepatic microsomal mixed function oxidase activity were observed. It was concluded that consumption of 2,4-dichlorophenol at mean daily doses of 40-491 mg/kg does not cause significant toxicologic alterations in mice.

Female Sprague Dawley rats were exposed to 2,4-dichlorophenol in their drinking water at concentrations of 0, 3, 30, or 300 ppm (Exon et al., 1984). For prenatal exposure, dams were dosed continuously from 3 weeks of age through breeding and parturition; for combined prenatal and postnatal exposure, dams were dosed continuously from 3 weeks of age through breeding, parturition, and lactation, and the progeny were given drinking water containing 2,4-dichlorophenol until 13 weeks of age. Compared with those of controls, liver and spleen weights were increased in rats that received combined prenatal and postnatal exposure of up to 300 ppm 2,4-dichlorophenol, and spleen weights were increased in rats that received 300 ppm 2,4-dichlorophenol by prenatal exposure only. There were no microscopic changes in the liver, spleen, or thymus of 2,4-dichlorophenol-exposed rats compared with controls. Humoral immune responsiveness was enhanced and cell-mediated immunity was depressed in rats that received the combined prenatal and postnatal exposure. Phagocytic activity of macrophages in dosed groups was not significantly different from that in controls. It was suggested that the immune system may be a sensitive target for 2,4-dichlorophenol toxicity.

2,4-Dichlorophenol caused a 70% stimulation of oxygen uptake in rat brain homogenates at a concentration of 2.5×10^{-4} M, indicating that this chemical may interfere with oxidative phosphorylation (Farquharson et al., 1958). 2,4-Dichlorophenol was a much less potent uncoupler of oxidative phosphorylation in rat liver mitochondria than was pentachlorophenol (Weinbach and Garbus, 1965). With increasing chlorination, there is an increase in the toxicity (Farquharson et al., 1958) as well as the potency of chlorophenols to uncouple oxidative phosphorylation (Weinbach and Garbus, 1965). 2,4-Dichlorophenol was also found to inhibit passive chloride permeability in ox erythrocytes, a property shared by agents that uncouple oxidative phosphorylation (Motais et al., 1978), and to increase the conductance of biomolecular phospholipid membranes by selectively transporting hydrogen ions through the membrane (Liberman and Topaly, 1968). Thus, toxicity of chlorophenols may involve interference with mitochondrial oxidative phosphorylation or other energy-linked, membrane-dependent processes.

The LC_{50} of 2,4-dichlorophenol for rainbow trout is about 70 µg/liter, whereas that for catfish and goldfish varies from 260 to 1,700 µg/liter (Birge et al., 1979). Survival of fathead minnows was reduced after 28 days of exposure to 2,4-dichlorophenol at 460 µg/liter or more, whereas growth was reduced at 1,240 µg/liter (Holcombe et al., 1982).

Liver and kidney changes have been observed in toxicology studies of other chlorophenols. 2,4,5-Trichlorophenol administered daily by gavage to rabbits for 28 days produced liver and kidney lesions at doses of 100-500 mg/kg (McCollister et al., 1961). Dietary administration of 2,4,5-trichlorophenol to rats for 96 days at concentrations of 3,000 and 10,000 ppm (equivalent to about 0.3-1.0 g/kg per day) produced degenerative changes in the liver and kidney. Toxic injuries caused by 2-chlorophenol in rats include fatty infiltration of the liver, erythrocyte casts in the tubules of the kidney, and hemorrhages in the intestines (Deichmann and Keplinger, 1981).

Developmental Toxicity

Oral administration of 2,4-dichlorophenol in corn oil to pregnant F344 rats at doses of 0, 200, 375, or 750 mg/kg per day on days 6-15 of gestation caused a dose-related decrease in maternal weight gain (Rodwell et al., 1984). The incidence of embryonic death increased and fetal body weight decreased in the high dose group, but no evidence of teratogenicity was observed.

Continuous exposure of female Sprague Dawley rats to 2,4-dichlorophenol at 3-300 ppm in drinking water from 3 weeks of age through breeding and parturition did not appear to affect reproductive performance, including conception, litter size, pup birth weight, number of stillborn pups, or survival to weaning (Exon et al., 1984).

Commercial-grade pentachlorophenol was reported to be embryotoxic and fetotoxic in rats, causing dose-related increases in resorptions, subcutaneous edema, dilated ureters, and anomalies of the skull, ribs, vertebrae, and sternebrae (Schwetz et al., 1974a). The no-effect dose for commercial-grade pentachlorophenol in pregnant Sprague Dawley rats was 5 mg/kg per day. Commercial-grade and purified 2,3,4,6-tetrachlorophenol were fetotoxic (causing delayed ossification of skull bones) but not embryolethal or teratogenic in Sprague Dawley rats (Schwetz et al., 1974b). The no-effect dose for this chlorinated phenol was 10 mg/kg per day.

Sperm penetration of mouse ova in vitro was depressed by exposure to 2,5-, 3,4-, or 3,5-dichlorophenol but not by exposure to 2,4-dichlorophenol (Seyler et al., 1984). In addition, neither sperm penetration of ova nor sperm motility was affected by exposure of CD-1 mice to 2,4-dichlorophenol (50-500 mg/kg per day) in drinking water for 90 days.

Carcinogenicity

2,4-Dichlorophenol was found to act as a skin tumor-promoting agent with the same order of activity as phenol when topically applied to the back of female Sutter mice twice per week for 15-24 weeks (Boutwell and Bosch, 1959). The application of 2,4-dichlorophenol (25 µl of a 20% solution in benzene) began 1 week after a single initiating dose of 0.3% dimethylbenz[*a*]anthracene (DMBA) in benzene. Based on the applied dose that gave a maximal tumor response, phenol was about 20 times less active than croton oil as a mouse skin tumor-promoting agent. 2-Chlorophenol, 3-chlorophenol, and 2,4,5-trichlorophenol were also shown to act as promoting agents in similar studies, whereas 2,4,6-trichlorophenol and pentachlorophenol were inactive. No long-term toxicology or carcinogenesis studies with 2,4-dichlorophenol have been reported.

2,4,6-Trichlorophenol was found to be carcinogenic to F344 rats and B6C3F$_1$ mice when administered in feed for 2 years (NCI, 1979). Doses were 5,000 or 10,000 ppm for rats and male mice and 5,214 or 10,428 ppm (time-weighted average) for female mice (equivalent to about 250-750 mg/kg per day for rats and 500-1,500 mg/kg per day for mice). Dose-related increased incidences of lymphomas or leukemia (combined) in male rats and increased incidences of hepatocellular neoplasms in dosed male and female mice compared with those in controls were observed.

Carcinogenesis studies of pentachlorophenol were conducted by feeding diets containing 0, 100, or 200 ppm technical-grade pentachlorophenol (equivalent to about 17 or 35 mg/kg per day) or 0, 100, 200, or 600 ppm Dowicide EC-7 (equivalent to about 17, 35, or 116 mg/kg per day) to groups of B6C3F$_1$ mice of each sex for 2 years (NTP, 1989). Dose-related increased incidences of hepatocellular neoplasms and pheochromocytomas in male and female mice and increased incidences of hemangiosarcomas in the spleen and liver in dosed female mice compared with those in controls were observed.

Genetic Toxicology

Results of most tests for induction of gene mutation in bacterial systems by 2,4-dichlorophenol were negative (Simmon et al., 1977; Rasanen et al., 1977; Rapson et al., 1980; Probst et al., 1981). The one exception is the Haworth et al. (1983) study that, although finding no evidence for induction of gene reversion in *Salmonella typhimurium* strains TA98, TA100, or TA1537, did report an equivocal increase in revertant colonies in strain TA1535 when exposure to 2,4-dichlorophenol occurred in the presence of Aroclor 1254-induced male Syrian hamster liver S9 (Table 19). Haworth et al. (1983) also included test results from all the other dichlorophenols: 2,3-, 2,5-, 2,6-, 3,4-, and 3,5-dichlorophenol; all were negative in Salmonella except 3,5-dichlorophenol, which produced an equivocal response in strain TA100 in the presence of Aroclor 1254-induced male Syrian hamster liver S9. The general lack of mutagenicity in Salmonella by structural analogs of 2,4-dichlorophenol has been reported by others (Rasanen et al., 1977; Rapson et al., 1980; Nestmann et al., 1980).

2,6-Dichlorophenol also did not produce an increase in revertants when tested for mutagenic activity in *Saccharomyces cerevisiae* XV185-14C without S9 activation (Nestmann and Lee, 1983). 3,5-Dichlorocatechol, a potential intermediate metabolite of 2,4-dichlorophenol, has also been shown to be nonmutagenic in Salmonella (Rasanen et al., 1977; Rapson et al., 1980; Nazar et al., 1981). 2,4-Dichlorophenol was inactive in tests for induction of DNA repair (unscheduled DNA synthesis) in primary cultures of rat hepatocytes (Probst et al., 1981).

In plants, a low percentage of mitotic abnormalities (primarily delayed anaphases and a slight increase in chromosomal "stickiness") was reported in root tip cells from the monocot *Allium cepa* after up to 5 days of growth in tap water containing 1-50 ppm 2,4-dichlorophenol (Fiskesjo et al., 1981). However, about 11.8% of pollen mother cells from *Vicia faba* flower buds (a dicotyledon) treated with a 0.1% aqueous solution of 2,4-dichlorophenol exhibited increased meiotic irregularities such as chromosome stickiness, lagging chromosomes, and anaphase bridge formation (Amer and Ali, 1968). A second study in which 0.39 ppm 2,4-dichlorophenol in water was administered by spraying the plants for 5 consecutive days or by soaking seeds for 24 hours in the chemical solution also reported stickiness, chromosomal fragmentation and lagging, and bridge formation in dividing pollen mother cells (Amer and Ali, 1974). Treatment of *V. faba* root tip cells with 62.5 mg/liter 2,4-dichlorophenol resulted in mitotic abnormalities including stickiness, anaphase bridge formation, and lagging in 3.9% of the examined metaphase/anaphase cells (Amer and Ali, 1969).

Human Effects

Dermatoses, including photoallergic contact dermatitis, were reported in humans exposed to trichlorophenols and tetrachlorophenols (Deichmann and Keplinger, 1981). Acquired chloracne and porphyria were reported in workers involved in the manufacture of 2,4-dichlorophenol and 2,4,5-trichlorophenol (Bleiberg et al., 1964). The causal agent(s) of these diseases may also have been dioxin or furan contaminants.

The threshold odor and taste concentrations for 2,4-dichlorophenol were reported to be 40 and 0.3 µg/liter, respectively (USEPA, 1980).

Study Rationale

2,4-Dichlorophenol was selected for toxicology and carcinogenicity studies because it was found in drinking water at several locations in the United States and because it was known to have skin tumor-promoting activity in mice. The feed route of administration was selected because 2,4-dichlorophenol has a low solubility in water and because the most common route of human exposure is oral.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2,4-DICHLOROPHENOL

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

PROCUREMENT AND CHARACTERIZATION OF 2,4-DICHLOROPHENOL

2,4-Dichlorophenol (special laboratory-distilled, greater than 99% pure) was obtained from Dow Chemical USA in two lots (Table 1). Lot no. OCR-640-57 was obtained in two batches (on 6/26/78 and 11/16/81) which were analyzed separately. Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the 2,4-dichlorophenol studies are on file at NIEHS. Both lots were identified as 2,4-dichlorophenol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (representative spectra are presented in Figures 1 and 2) were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra).

Purity for both lots of the study chemical was determined by elemental analysis, Karl Fischer water analysis, titration in water for lot no. OCR-640-57 or in methanol for lot no. OCR-808-125 of the phenol group with 0.1 N sodium hydroxide, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed with two solvent systems: toluene:methanol (95:5) (system 1) and hexane:acetone (90:10) (system 2). Gas chromatography was performed with flame ionization detection and a 1% SP1240 DA column (system 1) or a 3% SP2100 column (system 2).

Cumulative data indicated that lot no. OCR-640-57, batch 1, was at least 99% pure. The results of elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values. Water content was 0.21%. Titration of the phenol group indicated a purity of 100.46%. Thin-layer chromatography revealed one trace impurity by both systems. Gas chromatography by system 1 showed two impurity peaks with a combined area 0.59% of the major peak area. Gas chromatography by system 2 showed two impurity peaks with a combined relative area of 0.04%.

Cumulative data indicated that lot no. OCR-640-57, batch 2, was at least 99% pure. The results of elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values. Water content was 0.056%. Titration of the phenol group indicated a purity of 100.5%. Thin-layer chromatography by system 1 showed two trace impurities, whereas system 2 revealed a single trace impurity. Gas chromatography by system 1 showed two impurity peaks, one eluting as a shoulder before the major peak and one after the major peak, with a combined area 0.70% of the major peak area. Gas chromatography by system 2 showed a major peak and two impurity peaks with a combined area 0.20% of the major peak area.

TABLE 1. IDENTITY AND SOURCE OF 2,4-DICHLOROPHENOL USED IN THE FEED STUDIES

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers		
OCR-640-57, batch 1	OCR-640-57, batch 1	OCR-640-57, batches 1 and 2; OCR-808-125
Date of Initial Use		
8/11/79	4/14/80	Lot no. OCR-640-57: batch 1-- 3/4/81; batch 2-- 12/28/81; lot no. OCR-808-125--3/22/82
Supplier		
Dow Chemical USA (Midland, MI)	Dow Chemical USA (Midland, MI)	Dow Chemical USA (Midland, MI)

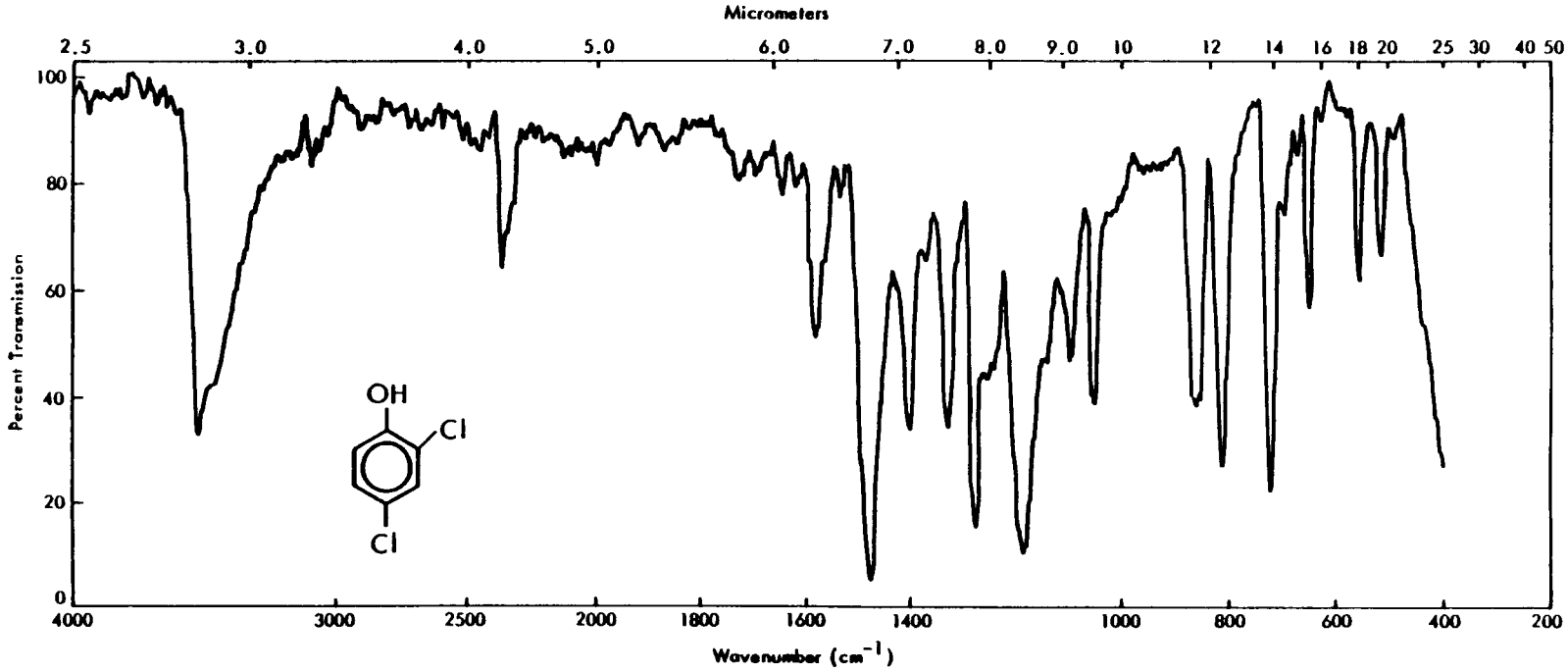


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 2,4-DICHLOROPHENOL (LOT NO. OCR-808-125)

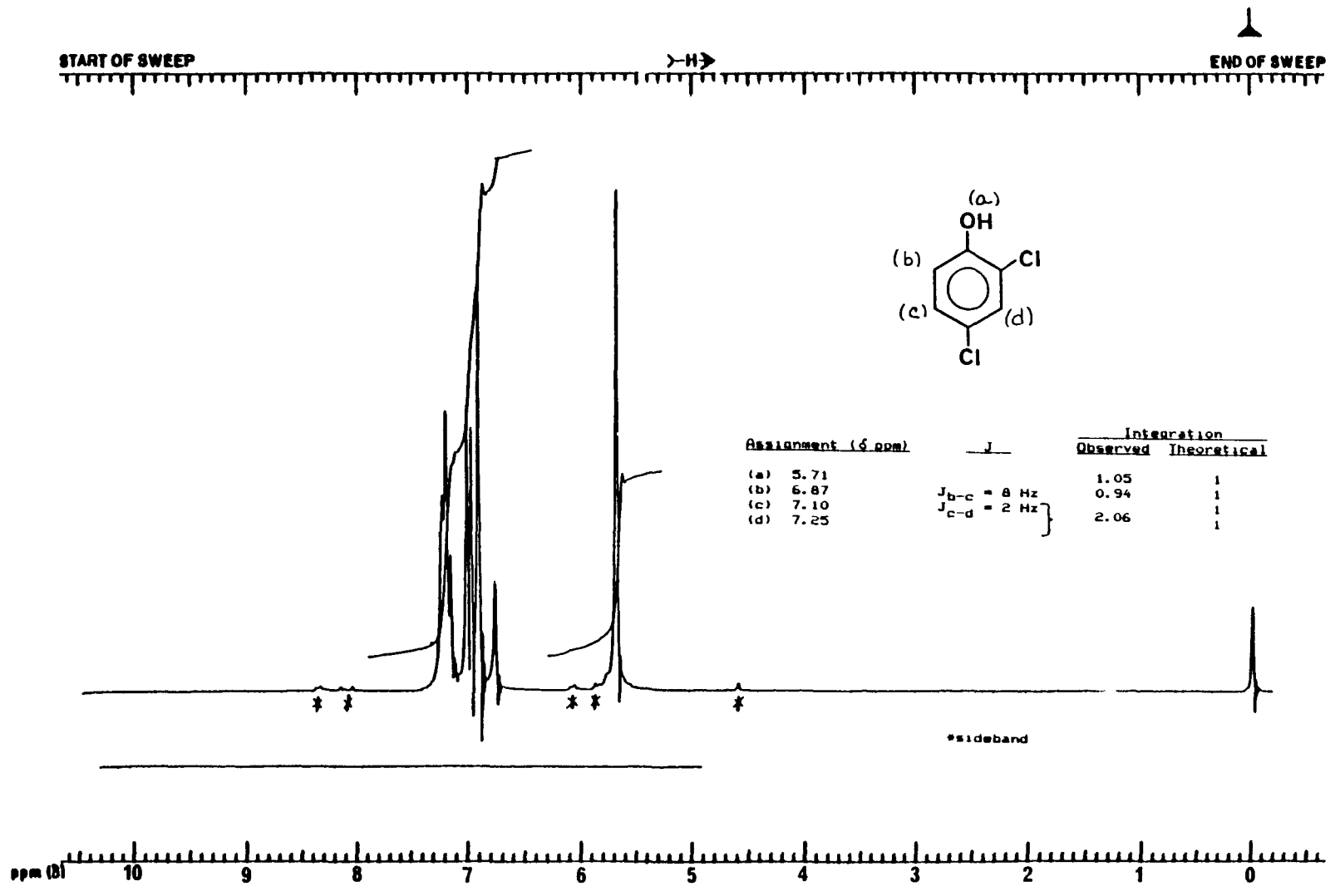


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2,4-DICHLOROPHENOL (LOT NO. OCR-808-125)

Cumulative data indicated a purity of approximately 99.5% for lot no. OCR-808-125. The elemental analyses for carbon, hydrogen, and chlorine agreed with the theoretical values. Water content was no more than 0.04%. Titration of the phenol group indicated a purity of 99.9%. Thin-layer chromatography by system 1 revealed two trace impurities, whereas system 2 indicated one trace impurity. Gas chromatography by system 1 showed three impurity peaks with a combined area 0.23% of the major peak area. Gas chromatography by system 2 showed one impurity peak with a relative area of 0.01%.

The supplier of the chemical provided data for the analysis of impurities of lot no. DC-62778 (not used in these studies). These analyses indicated that this lot of 2,4-dichlorophenol was 99.3% pure and contained 0.1% 1,4-dichlorophenol and 0.5% 2,6-dichlorophenol. Hexachlorobenzene was not found in this lot at a detection limit of 1 ppm. The following dioxins and furans were analyzed for but not detected in this particular lot:

Chemical	Limit of Detection (ppb)
Tetrachlorodibenzodioxin	1
Pentachlorodibenzodioxin	1
Hexachlorodibenzodioxin	1
Heptachlorodibenzodioxin	1
Octachlorodibenzodioxin	1
Tetrachlorodibenzofuran	10
Pentachlorodibenzofuran	10
Hexachlorodibenzofuran	10
Heptachlorodibenzofuran	10
Octachlorodibenzofuran	10

No analytical data for lot no. OCR-808-125 were provided by the supplier.

Stability studies were performed by gas chromatography with the same column as described above for system 2 and with solutions of 2,4-dichlorophenol in methanol containing 0.25% undecane as an internal standard. 2,4-Dichlorophenol was found to be stable as the bulk chemical when stored at temperatures of 5° C or lower for 2 weeks. There was some indication of decomposition at 25° C. The bulk chemical was stored at 4° C. Results of periodic analysis of the bulk chemical by infrared spectroscopy, potentiometric titration with sodium hydroxide, and gas chromatography indicated that no notable degradation occurred throughout the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diets were made by preparing a 2,4-dichlorophenol/feed premix from feed wetted with an acetone (technical grade) solution of the chemical (Table 2). Acetone was removed from the premix with a rotary evaporator; the premix then was blended with feed for 15 minutes. Studies to determine the homogeneity of a formulated diet mixture indicated a less than 4% deviation from the target concentration for samples taken from three locations in the blender after 10 minutes of mixing; homogeneity was not

TABLE 2. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF 2,4-DICHLOROPHENOL

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate amount of 2,4-dichlorophenol dissolved in 10-75 ml acetone and combined with 500 g feed; acetone then removed with a roto-evaporator. The premix added to required amount of feed in a Patterson-Kelly® Twin-Shell V blender and mixed for 15 min	Appropriate amount of chemical dissolved in 200 ml acetone and combined with 500-800 g feed; acetone then removed with a roto-evaporator. The premix added to required amount of feed in a Patterson-Kelly® Twin-Shell V blender and mixed for 15 min	Appropriate amount of chemical melted in 50°-55° C water bath, dissolved in 250-500 ml acetone, and combined with 600-1,000 g feed; acetone then removed with a roto-evaporator. The premix added to required amount of feed in a 16-qt Patterson-Kelly® Twin-Shell blender and mixed for 15 min. Control diets similarly treated with acetone
Maximum Storage Time		
8 d	2 wk	2 wk
Storage Conditions		
4° C	4° C	4° C

improved after 15 minutes of mixing. The recovery of 2,4-dichlorophenol from formulated diets by methanol extraction, although essentially complete immediately after preparation, decreased with time to about 58% after 7 days. The addition of 1% hydrochloric acid to the methanol extracting solvent resulted in only a marginal improvement in the amount recovered. Consequently, for the study of compound stability in feed, acid digestion of the feed mixtures was carried out before extraction with ether:hexane (1:1), and a recovery of 88% from feed samples stored for 2 weeks at 25° C was obtained. 2,4-Dichlorophenol at a concentration of 4,000 ppm in feed was stable for 5 weeks at −20° C. Recovery of 2,4-dichlorophenol from the feed mixture stored under these conditions was 95% relative to the zero-time recovery. For different samples of this feed mixture stored for 2 weeks at 5° C, recovery of 2,4-dichlorophenol was 93%. In the 13-week and 2-year studies, formulated diets were stored at 4° C for no longer than 2 weeks.

Periodic analyses of formulated diet mixtures of 2,4-dichlorophenol were conducted at the study laboratory and the analytical chemistry laboratory. Feed samples were extracted with methanol, centrifuged, and analyzed by gas chromatography with the same column as described before for system 1, with phenol in methanol as an internal standard. Formulated diets were analyzed once during the 13-week studies. The results were within specifications and ranged from 92.2% to 105.6% of the target concentrations (Table 3).

During the 2-year studies, the formulated diets were analyzed at approximately 8-week intervals and were within ±10% of the target concentrations approximately 82% (42/51) of the time throughout the 2-year studies (Table 4). Referee analyses were periodically performed by the study and analytical chemistry laboratories; results between the laboratories varied from 1% to 6% (Table 5).

TABLE 3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF 2,4-DICHLOROPHENOL (a)

Concentration of 2,4-Dichlorophenol in Feed (ppm)		Determined as a Percent of Target
Target	Determined (b)	
(c) 40,000	37,750	94.4
(d) 40,000	37,730	94.3
(e) 40,000	37,790	94.5
20,000	18,440	92.2
10,000	9,440	94.4
5,000	4,880	97.6
(c) 2,500	2,510	100.4
(d) 2,500	2,640	105.6
(e) 2,500	2,570	102.8

(a) Date mixed: 6/17/80
(b) Results of duplicate analysis
(c) Samples taken from bottom of blender
(d) Samples taken from top right of blender
(e) Samples taken from top left of blender

TABLE 4. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

Date Mixed	Concentration of 2,4-Dichlorophenol in Feed for Target Concentration (ppm) (a)		
	2,500	5,000	10,000
03/10/81	2,550	4,700	10,050
04/24/81	2,600	4,800	9,050
06/24/81	2,350	(b) 4,450	(b) 8,550
07/07/81	2,450	5,000	9,650
08/11/81	2,400	(c) 4,400	(c) 8,450
08/17/81	2,420	5,060	9,940
10/13/81	2,610	4,920	10,300
12/08/81	(c) 2,250	4,500	9,200
12/15/81	2,480	4,880	
02/18/82	2,350	4,900	9,450
04/06/82	2,450	4,900	9,250
06/03/82	2,450	4,950	10,650
07/27/82	(c) 1,560	(c) 3,910	9,000
08/03/82	2,380	4,520	9,220
09/21/82	(c) 2,190	(c) 4,230	9,120
09/28/82	(d) 2,560	(d) 5,000	
11/17/82	2,309	4,951	9,459
01/05/83	2,728	5,635	10,920
01/07/83		4,750	
Mean (ppm)	2,384	4,748	9,516
Standard deviation	251.2	377.4	699.1
Coefficient of variation (percent)	10.5	8.0	7.3
Range (ppm)	1,560-2,728	3,910-5,635	8,450-10,920
Number of samples	17	18	16

(a) Results of duplicate analysis
(b) Out of specifications
(c) Out of specifications; not used in the studies.
(d) Remix; not included in the mean.

TABLE 5. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
04/24/81	2,500	2,600	2,450
12/08/81	10,000	9,200	9,730
06/03/82	5,000	4,950	4,890
11/17/82	10,000	9,459	9,950

(a) Results of duplicate analysis
(b) Results of triplicate analysis

II. MATERIALS AND METHODS

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 15 days before the studies began. The rats were 6 weeks old when placed on study, and the mice were 7 weeks old.

Groups of five rats and five mice of each sex were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm 2,4-dichlorophenol for 14 consecutive days. Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed twice per day and weighed on days 0, 7, and 14. A necropsy was performed on all animals. Further experimental details are summarized in Table 6.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 2,4-dichlorophenol and to determine the concentrations to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 24 days, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and control groups according to another table of random numbers. Groups of 10 males and 10 females of each species were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm 2,4-dichlorophenol for 13 weeks. Further experimental details are summarized in Table 6.

Animals were observed twice per day; moribund animals were killed. Feed consumption was measured by cage. Individual animal weights were recorded once per week. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 5,000, or 10,000 ppm 2,4-dichlorophenol were fed to groups of 50 male rats and 50 male and 50 female mice for 103 weeks. Groups of 50 female rats received diets containing 0, 2,500, or 5,000 ppm.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female $\times$ 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 colonies 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. Animals were shipped to the study laboratory at 5-6 weeks of age and were quarantined for approximately 2 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-8 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).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF 2,4-DICHLOROPHENOL

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm 2,4-dichlorophenol in feed	Same as 14-d studies	Rats--male: 0, 5,000, or 10,000 ppm 2,4-dichlorophenol in feed; female: 0, 2,500, or 5,000 ppm; mice--0, 5,000, or 10,000 ppm
Date of First Dose		
8/11/79	4/14/80	Rats--3/4/81; mice--3/11/81
Date of Last Dose		
8/25/79	7/13/80	Rats--2/22/83; mice--3/1/83
Duration of Dosing		
14 consecutive d	13 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter; feed consumption measured	Same as 14-d studies	Observed 2 × d; weighed 1 × wk for 13 wk and then 1 × mo; feed consumption measured 1 × mo
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams not performed	Necropsy performed on all animals; histologic exams performed on all control and 40,000-ppm animals, all 20,000-ppm mice, and all animals dying before the terminal kill; the following tissues were examined: adrenal glands, blood smear, bone marrow, brain, colon, costochondral junction (rib), duodenum, ears, esophagus, eyes, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroid glands, pituitary gland, prostate/seminal vesicles/testes or ovaries/uterus, rectum, regional lymph nodes, salivary glands, sciatic nerve, skin, spinal cord, spleen, stomach, thigh muscle, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Bone marrow, colon, heart, jejunum, stomach, and urinary bladder examined from rats in the 10,000- and 20,000-ppm groups; femoral bone marrow examined from the 2,500- and 5,000-ppm female rat groups; liver examined from the 2,500-, 5,000-, and 10,000-ppm mouse groups	Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups: adrenal glands, blood smear, brain, colon, esophagus, eyes, gallbladder (mice), gross lesions, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spleen, sternum or femur or vertebrae including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Tissues examined from low dose groups included liver, nose, pituitary gland, and thyroid gland for male rats; adrenal glands, lymph nodes, pancreas, and spleen for female rats; liver, prostate, spleen, and tarsal joints for male mice; and uterus for female mice
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF 2,4-DICHLOROPHENOL (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification Toe clip	Toe clip	Toe and ear clip
Time Held Before Study 15 d	24 d	Rats--14 d; mice--15 d
Age When Placed on Study Rats--6 wk; mice--7 wk	Rats--7 wk; mice--9 wk	Rats--7 wk; mice--8 wk
Age When Killed Rats--9 wk; mice--10 wk	Rats--21 wk; mice--22 wk	Rats--111 wk; mice--112 wk
Necropsy Dates Rats--8/27/79; mice--8/28/79	Rats--7/14/80-7/15/80; mice--7/15/80-7/16/80	Rats--2/28/83-3/3/83; mice--3/7/83-3/10/83
Method of Animal Distribution Animals distributed to weight classes and assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 14-d studies	Same as 14-d studies
Feed Rodent Laboratory Chow 5001® meal (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Absorb-dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as 14-d studies	Same as 14-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--70°-73° F; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as 14-d studies	Temp--53°-83° F; hum--29%-73%; fluorescent light 12 h/d; 15 room air changes/h

monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Cages were not rotated during the studies. Further details of animal maintenance are given in Table 6.

Clinical Examinations and Pathology

All animals were observed twice per day; clinical signs were recorded once per day for 21 months and then once per month. Body weights were recorded once per week for the first 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, 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 (Table 6) were performed on all high dose and control animals. 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 group 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: Body weight and feed consumption data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). Other data were recorded in the Toxicology Data Management System. 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.

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 high dose and low dose groups 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).

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.

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 *S. 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 triplicate plates 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.

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, Texas). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/ml. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to

thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

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

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

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

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

FOURTEEN-DAY STUDIES

All rats lived to the end of the studies (Table 7). Clinical signs recorded for rats that received 40,000 ppm 2,4-dichlorophenol included hunched posture, rough hair coats, and a dehydrated appearance. For male or female rats that received 40,000 ppm, the final mean body weights were lower than the initial mean body weights. The final mean body weight of rats that received 20,000 ppm was 19% lower than that of controls for males and 9% lower for females. Feed consumption by rats that received 40,000 ppm was about 20% that by controls during the first week of the studies and about 50% during the second week. Feed consumption by males at 20,000 ppm and females at all dietary concentrations was about 20%-50% lower than that by controls. The loss in body weight in the 40,000-ppm groups was probably due to the reduced palatability of the feed mixture at this concentration of 2,4-dichlorophenol. No compound-related lesions were observed at necropsy.

THIRTEEN-WEEK STUDIES

All rats lived to the end of the studies (Table 8). The final mean body weight of rats that received 20,000 or 40,000 ppm 2,4-dichlorophenol was 20% or 40% lower than that of controls for males and 11% or 21% lower for females. Feed consumption by rats in the 40,000-ppm groups was about 75%-85% that by controls. Rats that received 40,000 ppm had hunched posture and rough hair coats. Bone marrow atrophy was seen in all males and females at 20,000 and 40,000 ppm 2,4-dichlorophenol and in 6/10 females at 10,000 ppm. Both erythroid and myelocytic elements were depleted.

TABLE 7. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF 2,4-DICHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	123	205	+82		14.7	19.1
2,500	5/5	126	186	+60	91	11.9	18.4
5,000	5/5	122	201	+79	98	13.2	17.4
10,000	5/5	125	199	+74	97	14.8	16.5
20,000	5/5	128	166	+38	81	9.7	15.9
40,000	5/5	127	98	−29	48	2.5	8.0
FEMALE							
0	5/5	100	139	+39		16.7	14.5
2,500	5/5	99	138	+39	99	10.7	12.3
5,000	5/5	98	134	+36	96	12.5	11.8
10,000	5/5	99	133	+34	96	9.9	11.4
20,000	5/5	100	127	+27	91	7.8	11.2
40,000	5/5	101	92	−9	66	2.3	9.0

(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; not corrected for scatter.

TABLE 8. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF 2,4-DICHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	159 ± 3	346 ± 5	+187 ± 6		14.9	17.4
2,500	10/10	163 ± 3	344 ± 5	+181 ± 6	99	15.6	16.9
5,000	10/10	166 ± 4	337 ± 7	+171 ± 5	97	13.5	17.6
10,000	10/10	164 ± 4	327 ± 3	+163 ± 6	95	14.6	18.6
20,000	10/10	161 ± 3	278 ± 3	+117 ± 4	80	14.1	16.1
40,000	10/10	163 ± 3	206 ± 13	+43 ± 12	60	12.4	12.6
FEMALE							
0	10/10	129 ± 3	205 ± 4	+76 ± 4		12.6	12.5
2,500	10/10	132 ± 3	197 ± 2	+65 ± 3	96	11.9	12.1
5,000	10/10	130 ± 3	190 ± 3	+60 ± 2	93	9.8	11.7
10,000	10/10	131 ± 3	196 ± 4	+65 ± 3	96	12.2	12.3
20,000	10/10	130 ± 3	183 ± 2	+53 ± 2	89	10.1	11.5
40,000	10/10	129 ± 2	162 ± 2	+33 ± 2	79	10.3	10.1

(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.

Dose Selection Rationale: Because of lower weight gain and bone marrow atrophy at higher concentrations, dietary concentrations selected for rats for the 2-year studies were 5,000 and 10,000 ppm 2,4-dichlorophenol for males and 2,500 and 5,000 ppm for females.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male rats were generally 5%-11% lower than those of controls from week 3 to the end of the study (Table 9 and Figure 3). Mean body weights of high dose female rats were 6%-12% lower than those of controls from week 31 to the end of the study. The average daily feed consumption by rats in the low dose and high dose groups was 95% of that by the controls for males and 97% and 94% for females (Appendix F, Tables F1 and F2). The estimated daily mean consumption of 2,4-dichlorophenol was 210 or 440 mg/kg for low dose or high dose male rats and 120 or 250 mg/kg for low dose or high dose female rats. No compound-related clinical signs were observed.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

Weeks on Study	Control		Low Dose			High Dose		
	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				**5,000 ppm**			**10,000 ppm**	
0	121	50	121	100	50	120	99	50
1	157	50	157	100	50	153	97	50
2	177	50	177	100	50	172	97	50
3	215	50	214	100	50	205	95	50
4	239	50	236	99	50	226	95	50
5	256	50	253	99	50	240	94	50
6	271	50	266	98	50	255	94	50
7	276	50	280	101	50	270	98	50
8	289	50	284	98	50	275	95	50
9	299	50	294	98	50	284	95	50
10	309	50	302	98	50	291	94	50
11	311	50	311	100	50	297	95	50
12	324	50	323	100	50	307	95	50
13	326	50	321	98	50	310	95	50
18	359	50	351	98	50	335	93	50
22	387	50	375	97	50	360	93	50
27	402	50	385	96	50	368	92	50
31	420	50	403	96	50	384	91	50
36	433	50	412	95	50	395	91	49
41	441	50	422	96	50	404	92	49
45	453	50	432	95	50	412	91	49
50	459	50	442	96	50	416	91	49
54	464	50	444	96	50	423	91	49
58	467	50	445	95	50	427	91	49
63	470	49	451	96	48	428	91	49
68	469	49	454	97	46	424	90	48
72	468	48	452	97	46	421	90	48
76	469	48	451	96	45	425	91	47
81	465	47	451	97	43	425	91	47
85	469	46	439	94	41	419	89	46
89	466	45	448	96	39	415	89	43
93	464	44	443	95	37	421	91	41
97	456	35	433	95	31	417	91	34
101	443	34	422	95	27	409	92	32
103	438	33	436	100	25	415	95	32
FEMALE				**2,500 ppm**			**5,000 ppm**	
0	105	50	106	101	50	105	100	50
1	123	50	123	100	50	123	100	50
2	139	50	136	98	50	136	98	50
3	149	50	148	99	50	148	99	50
4	160	50	158	99	50	158	99	50
5	167	50	163	98	50	163	98	50
6	175	50	170	97	50	171	98	50
7	177	50	175	99	50	175	99	50
8	185	50	180	97	50	178	96	50
9	189	50	187	99	50	185	98	50
10	193	50	189	98	50	188	97	50
11	196	50	193	98	50	186	95	50
12	198	50	195	98	50	190	96	50
13	199	50	195	98	50	188	94	50
18	210	50	206	98	50	199	95	50
22	222	50	216	97	50	211	95	50
27	231	50	231	100	49	221	96	50
31	231	50	228	99	49	218	94	50
36	239	50	233	97	49	223	93	50
41	244	49	241	99	49	228	93	49
45	251	49	243	97	49	229	91	49
50	257	49	248	96	49	231	90	49
54	263	49	253	96	49	240	91	49
58	271	49	261	96	49	244	90	49
63	281	48	268	95	49	250	89	48
68	289	48	277	96	49	254	88	48
72	295	48	280	95	49	262	89	47
76	301	48	284	94	49	268	89	47
81	312	47	297	95	48	275	88	46
85	314	46	299	95	47	281	89	45
89	322	45	308	96	46	288	89	45
93	329	44	316	96	45	288	88	44
97	332	43	319	96	44	304	92	41
101	331	36	323	98	44	301	91	41
103	334	34	331	99	43	306	92	40

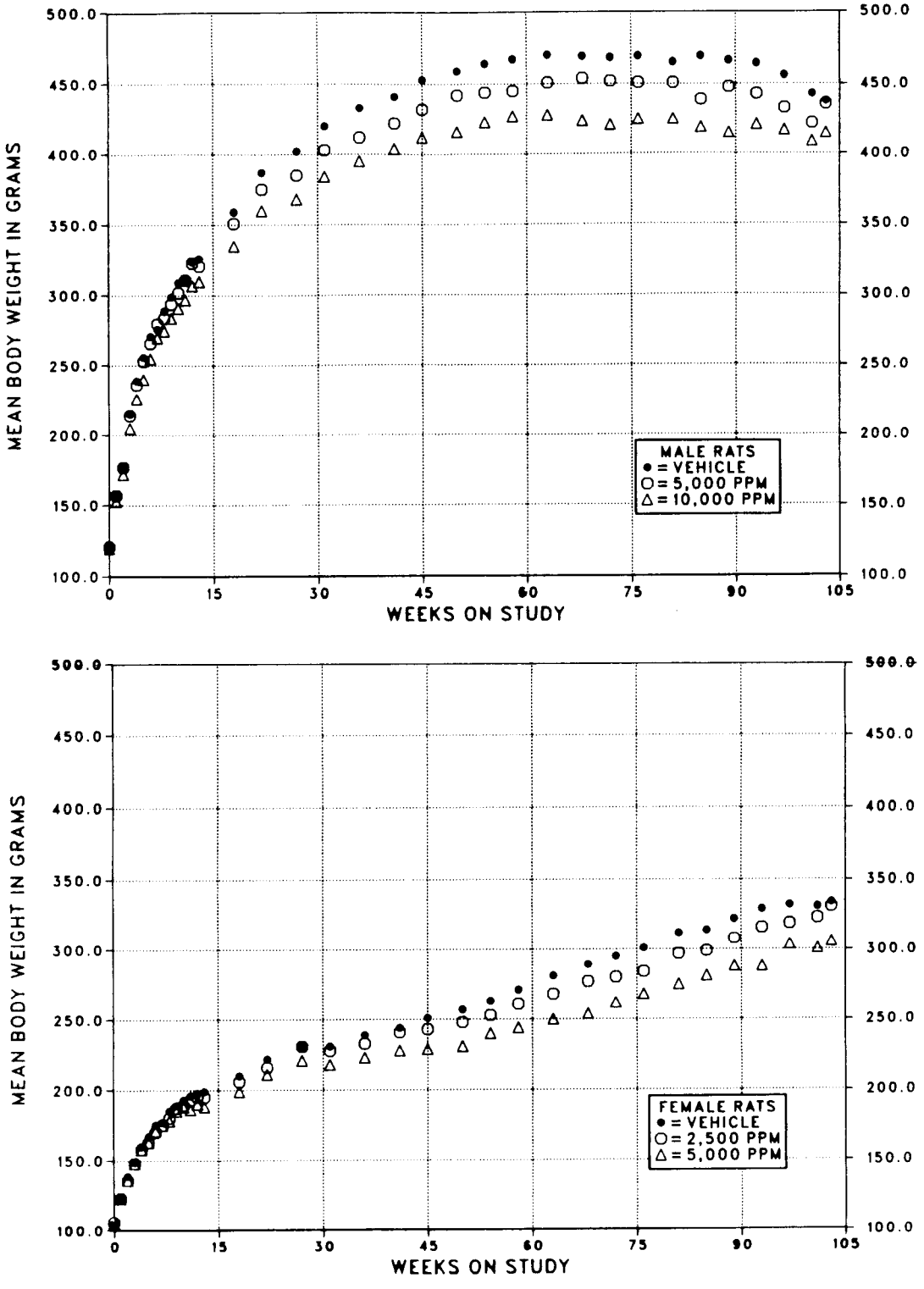


FIGURE 3. GROWTH CURVES FOR RATS FED DIETS CONTAINING 2,4-DICHLOROPHENOL FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing 2,4-dichlorophenol at the concentrations used in these studies and for controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nose and hematopoietic system.

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 rats, respectively.

Nose: The incidences of multifocal degeneration of the respiratory epithelium were increased in dosed male rats (control, 25/45; low dose, 38/48; high dose, 42/46). This lesion was characterized by the formation of small cysts and increased numbers of goblet cells within the epithelium and was located in the arch of the dorsal nasal meatus.

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

	Control	2,500 ppm	5,000 ppm	10,000 ppm
MALE (a)				
Animals initially in study	50		50	50
Nonaccidental deaths before termination (b)	17		25	18
Surviving until study termination	33		25	32
Survival P values (c)	0.877		0.148	0.939
FEMALE (a)				
Animals initially in study	50	50	50	
Nonaccidental deaths before termination (b)	16	7	10	
Surviving until study termination	34	43	40	
Survival P values (c)	0.234	0.066	0.319	

(a) First day of terminal-kill period: male--727; female--728
(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.

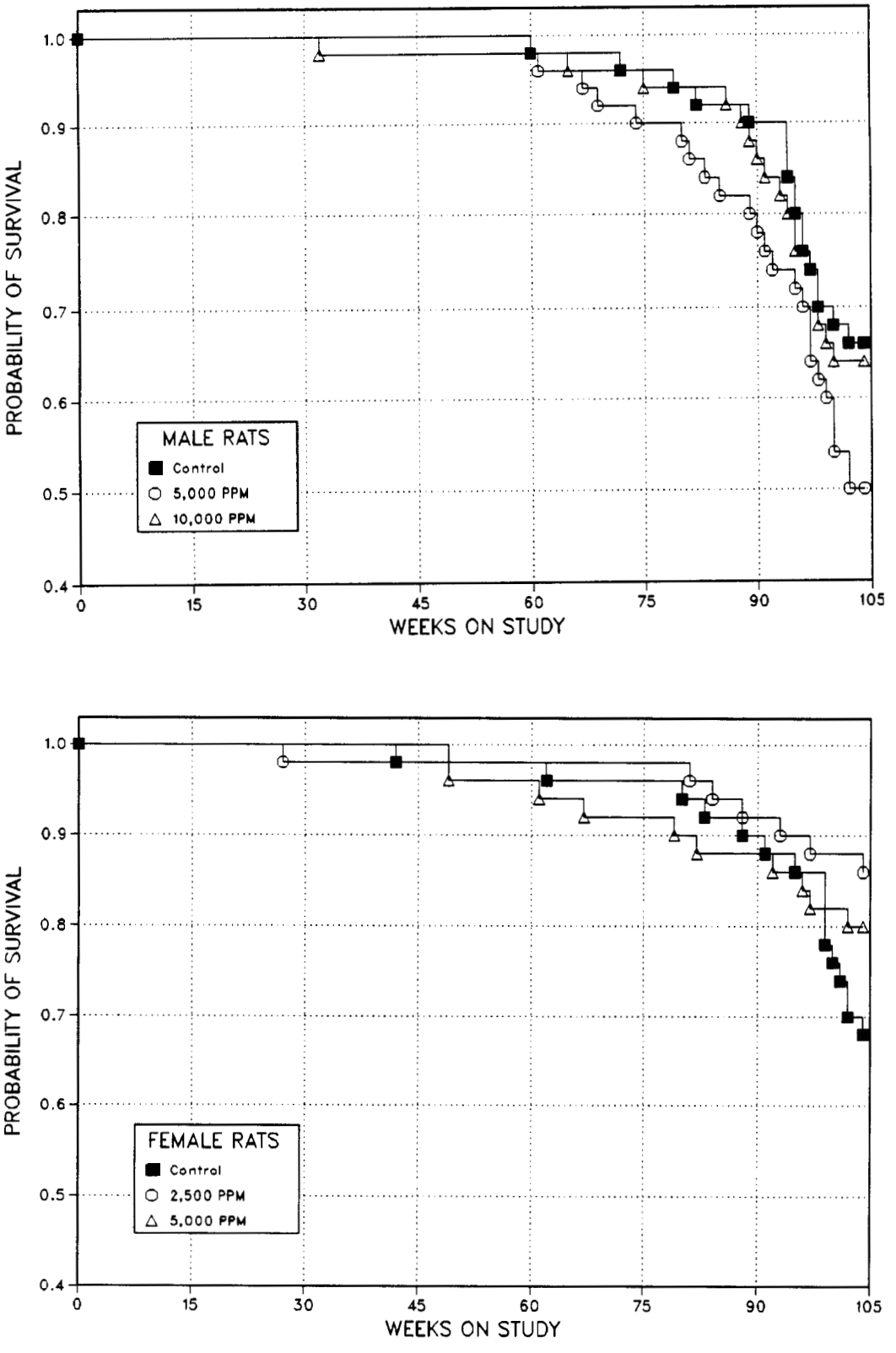


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING 2,4-DICHLOROPHENOL FOR TWO YEARS

Hematopoietic System: The incidences of mononuclear cell leukemia in dosed male rats were significantly lower than that in controls (Table 11). The incidences of mononuclear cell leukemia in control and dosed females were similar (control, 11/50; low dose, 7/50; high dose, 11/50).

TABLE 11. ANALYSIS OF MONONUCLEAR LEUKEMIA IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (a,b)

	Control	5,000 ppm (c)	10,000 ppm (c)
Overall Rates	31/50 (62%)	(d) 17/50 (34%)	17/50 (34%)
Adjusted Rates	68.2%	46.0%	41.2%
Terminal Rates	19/33 (58%)	7/25 (28%)	9/32 (28%)
Day of First Observation	419	469	454
Life Table Test	P=0.017N	P=0.089N	P=0.021N
Logistic Regression Test	P=0.003N	P=0.005N	P=0.004N

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) Historical incidence of leukemia at study laboratory (mean ± SD): 127/350 (36% ± 10%); historical incidence in NTP studies: 636/1,936 (33% ± 15%)
(c) The estimated dose in milligrams per kilogram per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix F.
(d) Gross lesions and target organs were examined in low dose animals according to protocol (see Table 6); 14 spleens were examined microscopically.

FOURTEEN-DAY STUDIES

One of five mice that received 40,000 ppm 2,4-dichlorophenol died before the end of the studies (Table 12). Mice that received 40,000 ppm 2,4-dichlorophenol were lethargic and had a dehydrated appearance. For male or female mice that received 40,000 ppm 2,4-dichlorophenol, the final mean body weights were lower than the initial mean body weights. There were no apparent compound-related effects on body weights of mice in the other dose groups. Feed consumption by mice that received 20,000 or 40,000 ppm was about half that by controls. No compound-related lesions were observed at necropsy.

TABLE 12. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF 2,4-DICHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	25.0	27.6	+2.6		7.3	6.7
2,500	5/5	26.4	29.0	+2.6	105.1	8.7	7.2
5,000	5/5	25.6	28.6	+3.0	103.6	7.6	5.7
10,000	5/5	26.6	29.8	+3.2	108.0	5.4	5.6
20,000	5/5	26.0	28.2	+2.2	102.2	3.0	3.7
40,000	(e) 4/5	25.8	20.8	−5.0	75.4	2.1	3.8
FEMALE							
0	5/5	18.0	20.0	+2.0		7.1	6.9
2,500	5/5	18.6	20.2	+1.6	101.0	6.3	7.2
5,000	5/5	18.6	21.0	+2.4	105.0	7.3	7.0
10,000	5/5	19.0	20.8	+1.8	104.0	6.3	6.9
20,000	5/5	18.2	19.6	+1.4	98.0	3.6	4.2
40,000	5/5	18.6	17.6	−1.0	88.0	2.4	3.8

(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; not corrected for scatter.
(e) Day of death: 4

THIRTEEN-WEEK STUDIES

All mice that received 40,000 ppm 2,4-dichlorophenol died in the first 3 weeks of the studies (Table 13). The final mean body weight of male mice that received 20,000 ppm was 12% lower than that of controls. Mean body weights of female mice in the 20,000-ppm group were about 10%-15% lower than those of controls for most of the study; this effect was not apparent at the end of the study, since the mean body weight of control female mice decreased by nearly 10% in the final week. There were no apparent compound-related adverse effects in the other groups of mice. Feed consumption by the 20,000- and 40,000-ppm groups was about 70%-80% of that by the controls at week 13. Rough hair coats were seen for male and female mice that received 10,000 ppm or more. A compound-related increase in the incidence of hepatocellular necrosis was observed in male mice (Table 14); the severity of this lesion in the 2,500-, 5,000-, and 10,000-ppm groups was minimal. Syncytial alteration, characterized by an increase in multinucleated hepatocytes, was also observed in the liver of dosed male mice. Renal tubular epithelial necrosis was observed in eight males and three females receiving 40,000 ppm.

TABLE 13. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF 2,4-DICHLOROPHENOL

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	(e) 9/10	25.3 ± 0.4	35.1 ± 0.9	+9.9 ± 0.6		7.0	7.3
2,500	(f) 9/10	24.7 ± 0.4	34.1 ± 0.6	+9.6 ± 0.7	97.2	11.0	7.3
5,000	10/10	25.0 ± 0.4	34.9 ± 0.8	+9.9 ± 0.6	99.4	10.9	7.4
10,000	10/10	24.5 ± 0.4	34.5 ± 0.6	+10.0 ± 0.4	98.3	3.8	5.7
20,000	10/10	24.4 ± 0.4	31.0 ± 0.3	+6.6 ± 0.3	88.3	3.7	4.5
40,000	(g) 0/10	24.1 ± 0.4	(h)	(h)	(h)	(h)	(h)
FEMALE							
0	10/10	20.3 ± 0.3	25.2 ± 0.6	+4.9 ± 0.5		12.7	7.8
2,500	10/10	21.1 ± 0.2	30.3 ± 0.8	+9.2 ± 0.6	120.2	12.9	7.1
5,000	10/10	20.8 ± 0.2	27.2 ± 0.6	+6.4 ± 0.5	107.9	13.1	10.2
10,000	10/10	20.6 ± 0.3	27.1 ± 0.3	+6.5 ± 0.4	107.5	9.6	6.2
20,000	10/10	20.2 ± 0.3	25.7 ± 0.5	+5.5 ± 0.3	102.0	3.6	5.4
40,000	(i) 0/10	20.2 ± 0.2	(h)	(h)	(h)	(h)	(h)

(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: 1
(f) Week of death: 9
(g) Week of death: 1,1,1,1,1,1,2,2,2,3
(h) No data are reported due to the 100% mortality in this group.
(i) Week of death: 1,1,1,1,1,1,2,3,3,3

TABLE 14. INCIDENCES OF LIVER AND KIDNEY LESIONS IN MICE IN THE THIRTEEN-WEEK FEED STUDIES OF 2,4-DICHLOROPHENOL

Site/Lesion	Concentration (ppm)					
	0	2,500	5,000	10,000	20,000	40,000
MALE						
Liver						
Necrosis	0/10	4/10	4/10	6/10	10/10	0/9
Syncytial alteration	0/10	0/10	0/10	10/10	10/10	0/9
Kidney						
Tubular necrosis	0/10	(a)	(a)	(a)	0/10	8/9
FEMALE						
Liver						
Necrosis	3/10	(a)	(a)	(a)	2/10	0/10
Kidney						
Tubular necrosis	0/10	(a)	(a)	(a)	0/10	3/10

(a) Not examined

Dose Selection Rationale: Because of the 100% mortality in mice of each sex at 40,000 ppm and hepatocellular necrosis in males, dietary concentrations of 2,4-dichlorophenol selected for mice for the 2-year studies were 5,000 and 10,000 ppm.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male mice were generally 3%-9% lower than those of controls between week 25 and week 86 (Table 15 and Figure 5). Mean body weights of high dose female mice were consistently and progressively lower than those of controls throughout the study. Mean body weights of low dose female mice were 5%-11% lower than those of controls from week 34 to the end of the study. The average daily feed consumption by mice in the low dose and high dose groups was 97% and 78% of that by the controls for males and 94% and 85% for females (Tables F3 and F4). The estimated daily mean consumption of 2,4-dichlorophenol was 800 or 1,300 mg/kg for low dose or high dose male mice and 430 or 820 mg/kg for low dose or high dose female mice. No compound-related clinical signs were observed.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

Weeks on Study	Control		5,000 ppm			10,000 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	21.9	50	22.0	100	50	22.0	100	50
1	24.3	50	23.6	97	50	24.4	100	50
2	25.6	50	25.5	100	50	26.1	102	50
3	27.0	50	26.2	97	50	26.5	98	50
4	28.0	50	27.8	99	50	28.1	100	50
5	29.0	49	28.6	99	50	28.7	99	50
6	29.8	49	29.2	98	50	29.3	98	50
7	30.7	49	30.2	98	50	30.0	98	50
8	30.4	49	30.0	99	50	30.3	100	50
9	31.2	49	29.5	95	50	30.7	98	50
10	31.6	49	31.2	99	50	31.4	99	50
11	31.3	49	30.4	97	50	31.2	100	50
12	32.2	49	32.3	100	50	31.9	99	50
13	32.3	49	31.9	99	50	31.1	96	50
17	32.1	48	31.7	99	49	32.2	100	50
21	33.7	48	34.3	102	48	34.2	101	50
25	34.2	48	34.0	99	48	33.2	97	49
30	36.7	48	36.0	98	48	35.6	97	49
34	37.8	48	37.2	98	48	36.0	95	49
38	38.4	48	38.3	100	48	35.4	92	48
43	38.3	48	38.1	99	48	36.2	95	47
47	38.0	48	38.7	102	48	34.6	91	46
51	39.9	48	39.2	98	48	37.5	94	46
56	39.1	48	38.0	97	48	36.0	92	44
61	40.2	48	38.1	95	47	38.3	95	38
66	39.3	48	38.0	97	47	38.1	97	38
70	38.7	48	38.2	99	44	38.4	99	37
74	39.7	48	38.6	97	43	37.7	95	37
78	39.5	48	38.0	96	42	37.4	95	36
82	39.1	47	37.4	96	42	36.0	92	36
86	37.2	44	38.0	102	42	36.4	98	34
90	39.3	43	38.0	97	41	38.2	97	34
95	39.1	41	37.3	95	38	36.8	94	33
99	37.7	36	37.2	99	34	37.4	99	31
103	38.9	33	37.7	97	33	38.2	98	31
FEMALE								
0	16.8	50	17.1	102	50	17.0	101	50
1	18.6	50	18.2	98	50	18.3	98	50
2	19.5	50	19.0	97	50	18.9	97	50
3	19.9	50	18.9	95	50	19.3	97	50
4	21.0	50	20.5	98	50	20.4	97	50
5	22.2	50	21.1	95	50	20.9	94	50
6	22.7	50	21.6	95	50	21.5	95	50
7	23.0	50	22.3	97	50	22.3	97	50
8	23.3	50	22.7	97	50	22.3	96	50
9	23.0	50	22.0	96	50	22.6	98	50
10	23.7	50	22.8	96	50	22.9	97	50
11	24.1	50	23.4	97	50	23.1	96	50
12	24.2	50	23.5	97	50	23.1	95	50
13	24.1	50	23.5	98	50	23.6	98	50
17	24.3	50	24.0	99	50	23.4	96	50
21	26.6	50	26.2	98	50	24.6	92	50
25	28.1	50	27.3	97	50	25.2	90	50
30	29.7	50	28.5	96	50	27.4	92	50
34	31.2	50	29.4	94	50	27.7	89	50
38	31.6	50	30.1	95	50	28.3	90	49
43	33.2	50	30.4	92	49	28.9	87	48
47	34.5	50	32.5	94	49	29.4	85	48
51	35.9	50	33.1	92	49	30.9	86	48
56	35.1	50	33.3	95	49	30.7	87	48
61	36.5	50	33.0	90	49	32.1	88	48
66	38.2	50	34.1	89	49	31.6	83	47
70	36.7	50	34.5	94	49	31.6	86	47
74	36.8	50	34.6	94	48	31.9	87	47
78	38.2	50	35.7	93	46	31.6	83	46
82	39.4	49	36.5	93	46	32.5	82	46
86	40.3	48	37.6	93	45	32.9	82	46
90	40.4	48	37.7	93	43	33.8	84	44
95	41.1	48	39.0	95	42	33.8	82	44
99	42.3	45	39.4	93	40	34.3	81	44
103	42.1	45	38.8	92	40	34.8	83	43

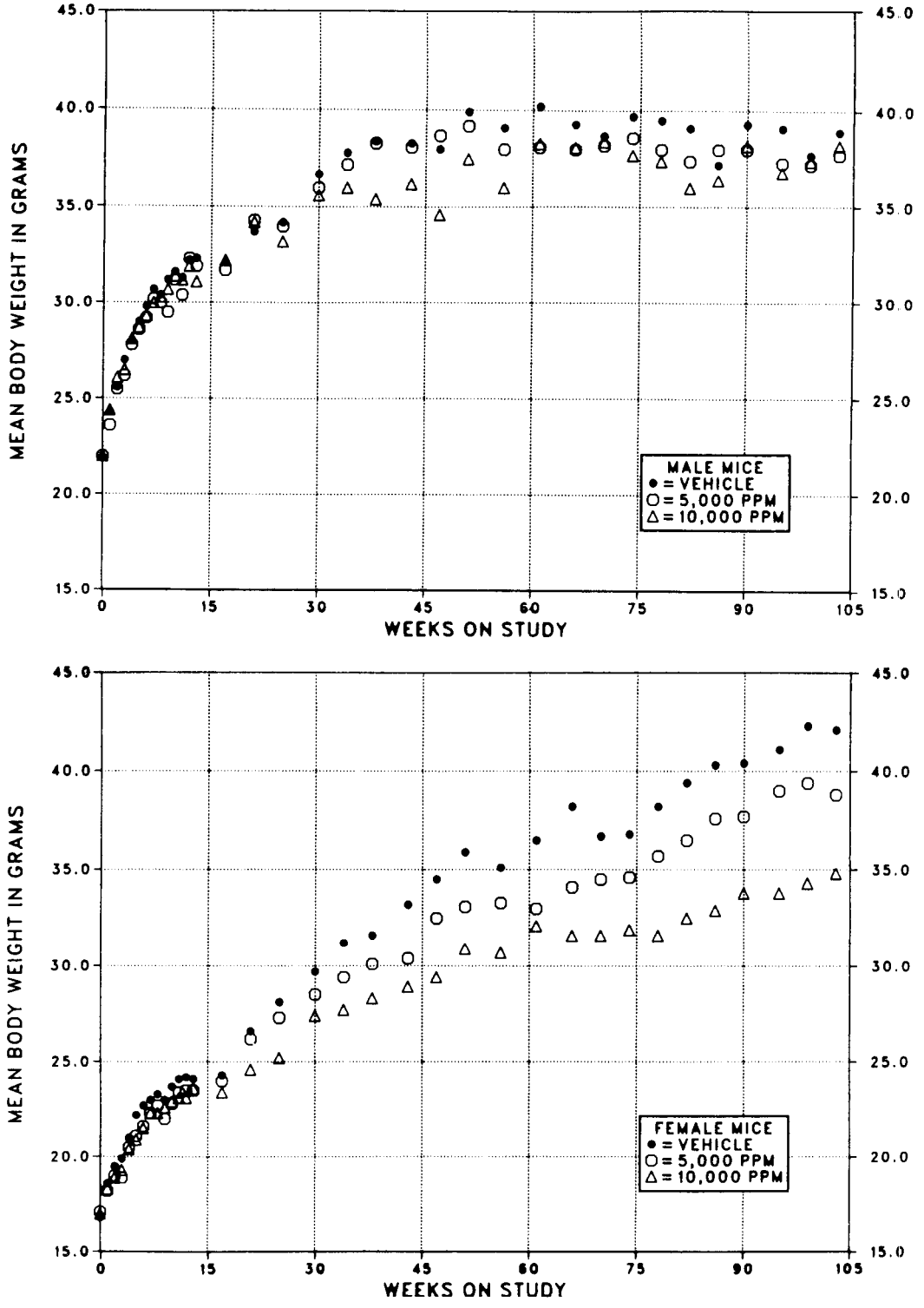


FIGURE 5. GROWTH CURVES FOR MICE FED DIETS CONTAINING 2,4-DICHLOROPHENOL FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing 2,4-dichlorophenol at the concentrations used in these studies and for controls are shown in Table 16 and in the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach, liver, and hematopoietic system.

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.

Forestomach: Squamous papillomas or squamous cell carcinomas of the forestomach occurred with a marginal positive trend in male mice (Table 17); two squamous papillomas and one squamous cell carcinoma of the forestomach were observed in the high dose group. The incidences of hyperplasia of the forestomach were nearly equal among the control and dosed groups of male mice. The incidence of squamous cell neoplasms of the forestomach was not increased in dosed female mice compared with that in controls.

Liver: Diffuse syncytial alteration of hepatocytes was observed at increased incidences in dosed male mice (control, 11/50; low dose, 33/49; high dose, 42/48). This change was characterized by individual hepatocytes with three or more nuclei. The number of affected cells was generally small, and the affected cells were widely scattered within the histologic sections.

Hematopoietic System: The incidence of malignant lymphomas in high dose female mice was significantly lower than that in controls (Table 18).

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

	Control	5,000 ppm	10,000 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	18	15
Accidentally killed	0	0	4
Animals surviving to study termination	33	32	31
Survival P values (c)	0.961	0.859	0.938
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	5	10	7
Animals surviving to study termination	45	40	43
Survival P values (c)	0.623	0.236	0.708

(a) First day of terminal-kill period: male--727; female--728
(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.

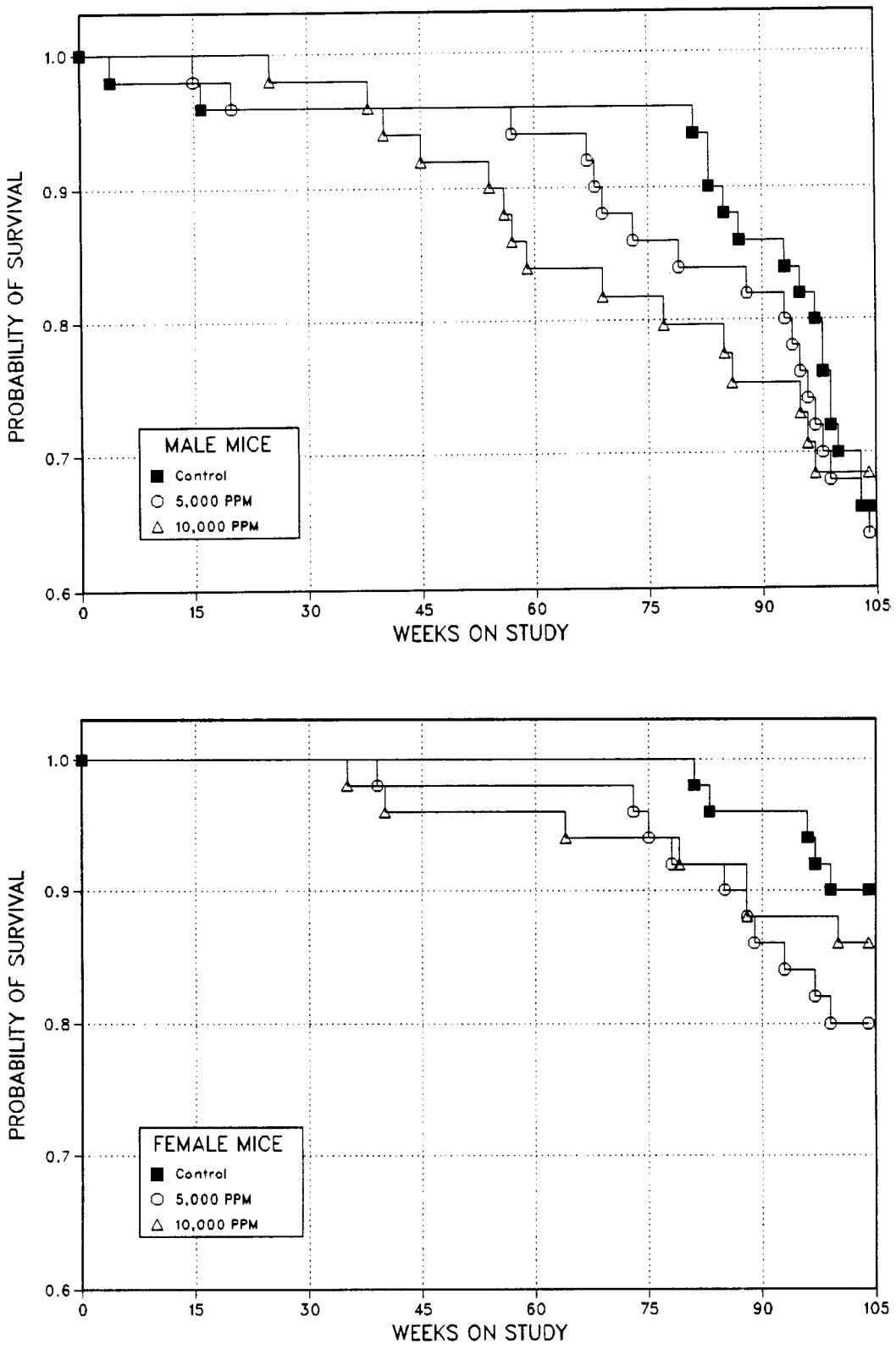


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING 2,4-DICHLOROPHENOL FOR TWO YEARS

TABLE 17. ANALYSIS OF FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL (a)

	Control	5,000 ppm (b)	10,000 ppm (b)
MALE			
Hyperplasia			
Overall Rates	5/50 (10%)	6/50 (12%)	4/50 (8%)
Squamous Papilloma or Squamous Cell Carcinoma (c)			
Overall Rates	0/50 (0%)	(d) 0/50	3/50 (6%)
Adjusted Rates	0.0%	0.0%	9.7%
Terminal Rates	0/33 (0%)	0/32 (0%)	3/31 (10%)
Day of First Observation			727
Life Table Tests	P=0.033	(e)	P=0.110
Logistic Regression Tests	P=0.033	(e)	P=0.110
FEMALE			
Hyperplasia			
Overall Rates	10/50 (20%)	10/50 (20%)	4/50 (8%)
Squamous Papilloma or Squamous Cell Carcinoma (f)			
Overall Rates	4/50 (8%)	(d) 3/50 (6%)	0/50 (0%)

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table D3 (footnotes).
(b) The estimated dose in milligrams per kilogram per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix F.
(c) Historical incidence of stomach squamous cell tumors at study laboratory (mean ± SD): 1/329 (0.3% ± 0.8%); historical incidence in NTP studies: 8/1,986 (0.4% ± 0.9%)
(d) Gross lesions and target organs were examined in low dose animals according to protocol (see Table 6).
(e) No P value is reported because no tumors were observed in the 5,000-ppm and control groups.
(f) Historical incidence of stomach squamous cell tumors at study laboratory (mean ± SD): 2/342 (0.6% ± 0.8%); historical incidence in NTP studies: 18/1,994 (0.9% ± 2%)

TABLE 18. ANALYSIS OF MALIGNANT LYMPHOMAS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (a)

	Control	5,000 ppm	10,000 ppm
Overall Rates	12/50 (24%)	(b) 6/50 (12%)	4/50 (8%)
Adjusted Rates	26.1%	14.1%	9.3%
Terminal Rates	11/45 (24%)	4/40 (10%)	4/43 (9%)
Day of First Observation	679	616	728
Life Table Tests	P=0.025N	P=0.156N	P=0.036N
Logistic Regression Tests	P=0.022N	P=0.118N	P=0.036N

(a) Historical incidence of lymphomas or leukemia (combined) at study laboratory (mean ± SD): 97/349 (28% ± 10%); historical incidence in NTP studies: 636/2,040 (31% ± 13%)
(b) Gross lesions and target organs were examined in low dose animals according to protocol (see Table 6); five livers and nine spleens were examined microscopically.

2,4-Dichlorophenol exhibited an equivocal response for mutagenicity in *Salmonella typhimurium* strain TA1535 when exposure occurred in the presence of Aroclor 1254-induced male Syrian hamster liver S9; the chemical produced no increases in revertant colonies in strains TA98, TA100, or TA1537 with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table 19). 2,4-Dichlorophenol increased the number of trifluorothymidine-resistant cells in the mouse L5178Y assay without exogenous metabolic activation; it was not tested in the presence of S9 (Table 20). In cytogenetic tests with cultured Chinese hamster ovary cells, 2,4-dichlorophenol caused a significant increase in the frequency of sister chromatid exchanges both in the presence and absence of S9 (Table 21) but did not induce chromosomal aberrations with or without Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table 22).

TABLE 19. MUTAGENICITY OF 2,4-DICHLOROPHENOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	115 ± 8.3	148 ± 7.5	121 ± 3.8	156 ± 4.1	104 ± 7.8	117 ± 18.1
	3.3	105 ± 7.3	146 ± 6.4	118 ± 0.7	134 ± 10.5	108 ± 5.2	146 ± 2.3
	10	117 ± 8.3	134 ± 2.6	129 ± 7.5	143 ± 4.8	101 ± 2.0	131 ± 6.1
	33	108 ± 9.0	144 ± 3.8	112 ± 9.7	141 ± 6.6	114 ± 6.7	145 ± 6.4
	100	113 ± 10.1	143 ± 1.5	152 ± 10.5	145 ± 4.9	130 ± 1.7	144 ± 7.6
	333	Toxic	Toxic	(c) 107 ± 9.3	(c) 124 ± 20.5	(c) 100 ± 15.3	(c) 87 ± 2.1
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control (d)		1,490 ± 67.6	2,172 ± 56.8	2500 ±59.8	1,086 ±81.9	1,171 ± 36.2	1,139 ± 57.5
TA1535	0	20 ± 2.3	27 ± 0.3	11 ± 3.2	8 ± 0.9	12 ± 1.5	10 ± 1.2
	3.3	13 ± 1.3	20 ± 4.3	9 ± 0.9	10 ± 0.9	8 ± 1.7	10 ± 1.2
	10	21 ± 1.2	23 ± 3.5	15 ± 1.7	10 ± 1.7	10 ± 1.5	9 ± 2.6
	33	24 ± 5.7	27 ± 2.9	13 ± 1.2	15 ± 2.5	15 ± 2.7	11 ± 1.3
	100	20 ± 1.5	30 ± 1.9	21 ± 1.5	14 ± 0.9	14 ± 1.8	15 ± 4.7
	333	Toxic	Toxic	(c) 21 ± 1.5	(c) 17 ± 0.7	(c) 18 ± 1.5	13 ± 2.0
Trial summary		Negative	Negative	Weakly positive	Equivocal	Negative	Negative
Positive control (d)		1,232 ± 47.6	1,876 ± 33.0	158 ± 3.7	71 ± 2.2	81 ± 11.3	64 ± 1.0
TA1537	0	9 ± 1.2	10 ± 2.8	11 ± 3.5	9 ± 1.5	12 ± 0.6	9 ± 1.8
	3.3	9 ± 1.8	9 ± 1.2	10 ± 0.7	13 ± 1.2	13 ± 1.0	8 ± 1.3
	10	8 ± 2.3	10 ± 1.2	12 ± 2.5	10 ± 2.0	10 ± 1.7	9 ± 1.2
	33	6 ± 0.3	9 ± 0.6	9 ± 1.5	8 ± 1.5	12 ± 1.2	7 ± 2.3
	100	6 ± 1.0	8 ± 1.5	8 ± 1.2	7 ± 0.3	13 ± 2.0	6 ± 0.7
	333	Toxic	Toxic	(c) 9 ± 0.6	9 ± 0.9	(c) 4 ± 0.6	(c) 5 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		700 ± 50.7	537 ± 386.0	278 ± 11.5	137 ± 5.8	133 ± 1.5	72 ± 3.6
TA98	0	19 ± 2.8	16 ± 1.0	28 ± 1.0	28 ± 2.3	23 ± 3.2	29 ± 0.6
	3.3	20 ± 2.3	22 ± 2.4	33 ± 1.2	32 ± 7.0	24 ± 2.0	24 ± 3.5
	10	28 ± 3.3	17 ± 0.7	30 ± 2.3	32 ± 5.6	31 ± 1.7	22 ± 6.2
	33	20 ± 3.6	23 ± 0.3	28 ± 3.7	24 ± 2.5	27 ± 3.8	28 ± 1.0
	100	18 ± 2.0	19 ± 0.0	24 ± 5.5	19 ± 1.2	25 ± 1.2	19 ± 4.0
	333	Toxic	(c) 10 ± 1.7	(c) 18 ± 3.1	21 ± 2.2	(c) 14 ± 0.3	17 ± 3.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		1,253 ± 20.3	1,827 ± 8.7	1,768 ± 33.0	1,639 ± 36.9	1,239 ± 12.8	1,385 ± 63.8

(a) Study performed at EG&G Mason Research Institute. The detailed protocol is presented in 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. High dose was limited by toxicity or solubility; 0 µg/plate dose is the solvent control.

(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 tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE 20. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY 2,4-DICHLOROPHENOL IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Ethanol (d)		83.8 ± 7.2	100.0 ± 2.7	69.0 ± 7.0	27.5 ± 2.3
2,4-Dichlorophenol	(e) 10	62.5 ± 10.5	64.5 ± 1.5	52.5 ± 6.5	29.5 ± 8.5
	(e) 20	52.5 ± 3.5	43.5 ± 9.5	43.5 ± 12.5	27.0 ± 6.0
	40	72.3 ± 7.8	53.0 ± 3.0	72.3 ± 8.7	34.0 ± 6.2
	(e) 50	64.0 ± 3.0	46.0 ± 4.0	70.0 ± 14.0	37.0 ± 9.0
	(e) 60	67.0 ± 5.0	36.0 ± 5.0	135.0 ± 28.0	(f) 69.0 ± 19.0
Methyl methanesulfonate	5	58.3 ± 3.8	43.3 ± 3.4	336.0 ± 25.5	(f) 192.3 ± 7.5
Trial 2					
Ethanol (d)		88.3 ± 7.7	100.0 ± 10.7	68.3 ± 7.4	26.3 ± 3.1
2,4-Dichlorophenol	20	64.7 ± 4.8	71.3 ± 7.7	62.7 ± 3.5	32.7 ± 4.7
	(g) 30	82.0 ± 10.0	22.5 ± 6.5	235.5 ± 32.5	(f) 99.0 ± 25.0
	(g) 40	66.5 ± 0.5	7.0 ± 0.0	324.0 ± 55.0	(f) 163.0 ± 26.0
	50	Lethal	--	--	--
Methyl methanesulfonate	5	58.3 ± 4.7	41.0 ± 4.6	472.0 ± 30.4	(f) 271.3 ± 5.5

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate unless otherwise specified; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency. All tests were performed in the absence of metabolic activation.

(b) Mean ± standard error of replicate trials for approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Data presented are the average of four tests.

(e) Data presented are the average of two tests.

(f) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(g) Data presented are the average of two tests; the dose in one test was lethal.

TABLE 21. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 2,4-DICHLOROPHENOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,021	550	0.54	11.0	25.5	
2,4-Dichlorophenol	0.167	50	1,033	588	0.57	11.8	25.5	107.3
	0.5	50	1,025	556	0.54	11.1	25.5	100.9
	1.67	50	1,029	708	0.69	14.2	(d) 33.5	129.1
	5	0						
Mitomycin C	0.001	50	1,034	720	0.70	14.4	25.5	130.9
	0.01	5	104	190	1.83	38.0	25.5	345.5
Trial 2--Summary: Equivocal								
Dimethyl sulfoxide		50	1,037	474	0.46	9.5	25.5	
2,4-Dichlorophenol	3	50	1,038	463	0.45	9.3	25.5	97.9
	4	50	1,031	515	0.50	10.3	25.5	108.4
	5	50	1,033	539	0.52	10.8	25.5	113.7
Mitomycin C	0.001	50	1,041	573	0.55	11.5	25.5	121.1
	0.01	5	103	239	2.32	47.8	25.5	503.2
Trial 3--Summary: Positive								
Medium		50	1,034	429	0.41	8.6	25.5	
2,4-Dichlorophenol	1.6	50	1,022	566	0.55	11.3	25.5	131.4
	3.1	50	1,031	606	0.59	12.1	25.5	140.7
	6.3	50	1,020	603	0.59	12.1	25.5	140.7
Mitomycin C	0.001	50	1,032	724	0.70	14.5	25.5	168.6
Trial 4--Summary: Positive								
Dimethyl sulfoxide		50	1,024	439	0.43	8.8	25.5	
2,4-Dichlorophenol	3.1	50	1,036	524	0.51	10.5	25.5	119.3
	6.3	50	1,038	559	0.54	11.2	(d) 31.5	127.3
	12.6	50	1,036	590	0.57	11.8	(d) 31.5	134.1
Mitomycin C	0.001	50	1,035	710	0.69	14.2	25.5	161.4
	0.01	5	104	231	2.22	46.2	25.5	525.0
+S9 (e)								
Summary: Positive								
Dimethyl sulfoxide		50	1,034	460	0.44	9.2	25.5	
2,4-Dichlorophenol	99.7	50	1,028	477	0.46	9.5	25.5	103.3
	120	50	1,035	612	0.59	12.2	25.5	132.6
	140.4	50	1,019	570	0.56	11.4	(d) 32.8	123.9
	160	0						
Cyclophosphamide	0.3	50	1,032	679	0.66	13.6	25.5	147.8
	2	5	104	208	2.00	41.6	25.5	452.2

TABLE 21. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 2,4-DICHLOROPHENOL (Continued)

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethylsulfoxide) as described in (c) and (e) 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 of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, 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) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. The cells were then 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 22. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 2,4-DICHLOROPHENOL (a)

−S9 (b)					+S9 (c)				
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
Harvest time 20.5 hours (d)					Harvest time 10.5 hours				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3.0		100	0	0.00	0.0
2,4-Dichlorophenol					2,4-Dichlorophenol				
40.2	100	4	0.04	3.0	100.5	100	0	0.00	0.0
50.3	100	6	0.06	5.0	125	100	1	0.01	1.0
75	100	5	0.05	5.0	150	100	2	0.02	2.0
					176	0			
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
62.5	50	22	0.44	34.0	25	50	7	0.14	12.0

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). 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.
(d) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.

IV. DISCUSSION AND CONCLUSIONS

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Toxicology and carcinogenesis studies of 2,4-dichlorophenol, a chemical intermediate used largely in the manufacture of the herbicide 2,4-dichlorophenoxyacetic acid, were conducted by administration of this chemical (greater than 99% pure) in NIH 07 Rat and Mouse Ration to male and female F344/N rats and $B6C3F_1$ mice. The selection of doses of 2,4-dichlorophenol for the 2-year studies, 5,000 or 10,000 ppm for male rats and male and female mice and 2,500 or 5,000 ppm for female rats, was based on results of the 13-week feed studies.

In the 13-week studies, rats and mice of each sex were administered 2,4-dichlorophenol in the diet at concentrations ranging from 2,500 to 40,000 ppm. 2,4-Dichlorophenol at these concentrations did not cause any deaths in rats; however, final mean body weights of male and female rats that received the higher doses of 2,4-dichlorophenol were more than 10% lower than those of controls. Bone marrow atrophy, involving both erythroid and myelocytic elements, was observed in these animals. In a drinking water study in which Sprague Dawley rats were administered 300 ppm 2,4-dichlorophenol in a combined in utero and postnatal exposure, chemical-related depression of cell-mediated immunity and enhancement of humoral immune responsiveness were observed; however, no compound-related effects in the bone marrow were reported (Exon et al., 1984). The doses of 2,4-dichlorophenol used in the study by Exon et al. (1984) were much lower than those that caused bone marrow atrophy in the present studies. For the current 2-year studies of 2,4-dichlorophenol in rats, dietary concentrations were selected (5,000 and 10,000 ppm for males and 2,500 and 5,000 ppm for females) which did not appreciably affect body weight gain or produce bone marrow atrophy in the 13-week studies. Bone marrow atrophy was observed in female rats that received 10,000 ppm 2,4-dichlorophenol for 13 weeks but not in male rats receiving that concentration.

Dietary administration of 2,4-dichlorophenol to $B6C3F_1$ mice for 13 weeks caused deaths of all animals in the 40,000-ppm groups and a reduction in mean body weight gain in the 20,000-ppm groups. The most notable toxicologic lesion in mice that survived until the end of the study was hepatocellular necrosis in males (see Table 14). The incidence and severity of this lesion increased with dose. In the 2,500-, 5,000-, and 10,000-ppm groups, the severity of the hepatocellular necrosis was considered to be minimal. Syncytial alteration (multinucleated hepatocytes) was also observed in the liver of dosed male mice. Neither hepatocellular necrosis nor syncytial alteration was reported in the liver of ICR mice fed diets containing 200-2,000 ppm 2,4-dichlorophenol for 6 months (Kobayashi et al., 1972) or of CD-1 mice exposed for 90 days to 2,4-dichlorophenol in drinking water at concentrations of 200-2,000 ppm (Borzelleca et al., 1985b). The doses of 2,4-dichlorophenol in those studies were lower than those that produced hepatocellular necrosis or multinucleated hepatocytes in $B6C3F_1$ mice in the current studies (see Table 14). For the 2-year studies of 2,4-dichlorophenol in mice, dietary concentrations were selected (5,000 and 10,000 ppm for males and females) which in the 13-week studies did not appreciably affect body weight gain or produce potentially life-threatening hepatocellular necrosis.

The 2-year studies of 2,4-dichlorophenol in F344/N rats and $B6C3F_1$ mice were remarkable because few chemical-related effects were observed. There were no significant differences in survival between any groups of rats or mice of either sex. Mean body weights of dosed male and female rats were about 5%-10% lower than those of controls. Similar effects of compound administration on body weight were observed in the studies in mice, except that the mean body weights of high dose female mice were about 10%-20% lower than those of controls.

There were no increased incidences of neoplastic lesions in dosed male or female rats compared with those in controls. A reduction in the incidence of mononuclear cell leukemia was observed in high dose male rats compared with that in controls; however, this change was not considered to be necessarily related to exposure to 2,4-dichlorophenol, since the incidence of leukemia in high dose male rats was similar to the historical incidence of leukemia in untreated F344/N male rats (Table A4). The incidence of leukemia in control male rats was nearly twice that generally observed.

In male mice given diets containing 2,4-dichlorophenol for 2 years, two squamous papillomas and one squamous cell carcinoma of the forestomach were observed in three animals in the high dose group. Squamous cell neoplasms of the forestomach are uncommon in untreated $B6C3F_1$ mice (historical incidence in NTP studies: 0.4% [8/1,986] for males and 0.9% [18/1,994] for females). However, because there was a negative trend for squamous cell neoplasms in female mice, with an unusually high incidence in controls (8%), and because there was no apparent effect of 2,4-dichlorophenol on the incidence of hyperplasia of the forestomach in male mice, the three forestomach neoplasms observed in male mice were not considered to be caused by 2,4-dichlorophenol. Chemical-induced neoplasia of the forestomach generally is not sex specific.

Syncytial alteration of hepatocytes, a chemical-related effect noted in the 13-week study, was also observed at increased incidences in dosed male mice in the 2-year study. 2,4-Dichlorophenol may block normal cell division in mouse hepatocytes by reducing the levels of ATP.

The only histopathologic change observed in female mice was a decrease in the incidence of malignant lymphomas in the high dose group compared with that in the controls. This decrease may not have been due to exposure to 2,4-dichlorophenol, since malignant lymphomas in female $B6C3F_1$ mice are common and the change in incidence in this study was only marginally significant.

In 2-year feed studies of other chlorophenols, 2,4,6-trichlorophenol was carcinogenic for F344 rats and $B6C3F_1$ mice (NCI, 1979), and technical-grade pentachlorophenol caused cancer in $B6C3F_1$ mice (rats were not studied) (NTP, 1989). The doses of 2,4-dichlorophenol used in the present 2-year studies were similar to those used in the 2,4,6-trichlorophenol studies and about 20 times greater than those used in the pentachlorophenol studies. The reason for the difference in carcinogenicity between 2,4-dichlorophenol and 2,4,6-trichlorophenol or technical-grade pentachlorophenol is not readily apparent. Although the relative toxicities of the various chlorophenols may be related to differences in their potency as uncouplers of mitochondrial oxidative phosphorylation (Farquharson et al., 1958; Weinbach and Garbus, 1965), it is unlikely that this factor was critical in the carcinogenic responses to the chlorophenols in rats or mice, since doses selected for the 2-year studies of these compounds varied, based on their toxicologic potential. In a skin tumor-promoting study, 2,4-dichlorophenol, but not 2,4,6-trichlorophenol or pentachlorophenol, was found to promote DMBA-initiated skin tumors in mice (Boutwell and Bosch, 1959).

Negative responses observed in NTP-sponsored mutagenicity assays with bacteria on 2,4-dichlorophenol, 2,4,6-trichlorophenol, and pentachlorophenol corroborate similar negative results reported by others (Simmon et al., 1977; Rasanen et al., 1977; Rapson et al., 1980; Nestmann et al., 1980; Probst et al., 1981; Haworth et al., 1983). Furthermore, all of the chlorinated phenols tested by the NTP, including three chlorophenols, six dichlorophenols, six trichlorophenols, three tetrachlorophenols, and pentachlorophenol, gave negative responses in the Salmonella assay. These results indicate that chlorinated phenols lack mutagenic activity in Salmonella.

However, NTP-sponsored cytogenetic tests with cultured Chinese hamster ovary (CHO) cells did exhibit a mixture of positive and negative responses with the seven chlorinated phenols tested to date. An increase in chromosomal aberrations was produced by 2,3,4- and 2,3,6-trichlorophenol, 2,3,5,6-tetrachlorophenol, and pentachlorophenol but not by 2,4-dichlorophenol, 2,4,6-trichlorophenol, or 3,4,5-trichlorophenol. An increase in sister chromatid exchanges was produced by 2,4-dichlorophenol, 2,3,4-trichlorophenol, 2,3,5,6-tetrachlorophenol, and pentachlorophenol but not by 2,3,6-, 2,4,6-, or 3,4,5-trichlorophenol. No relationship between the observed responses and either the number or position of the chlorine atoms is apparent from these results. In addition, no apparent relationship is evident between the responses observed in the cytogenetic tests in CHO cells with 2,4-dichlorophenol and the negative carcinogenic activity in rats and mice.

The experimental and tabulated data for the NTP Technical Report on 2,4-dichlorophenol

were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, 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.

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** for male F344/N rats fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol or for female F344/N rats fed diets containing 2,500 or 5,000 ppm 2,4-dichlorophenol. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice fed diets containing 5,000 or 10,000 ppm 2,4-dichlorophenol.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(47)	*(50)	(47)
Leukemia mononuclear	1 (2%)		
Colon, Peyer's patch, leukemia mononuclear	3 (6%)		
Peyer's patch, rectum, leukemia mononuclear	1 (2%)		
Rectum, leukemia mononuclear	1 (2%)		
Intestine small	(47)	*(50)	(47)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Leukemia mononuclear	1 (2%)		
Ileum, Peyer's patch, leukemia mononuclear			1 (2%)
Jejunum, sarcoma	1 (2%)		
Jejunum, Peyer's patch, leukemia mononuclear	3 (6%)		
Peyer's patch, leukemia mononuclear	2 (4%)		
Liver	(50)	(50)	(50)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Hepatocellular carcinoma	3 (6%)	1 (2%)	
Leukemia mononuclear	31 (62%)	16 (32%)	17 (34%)
Neoplastic nodule	3 (6%)		1 (2%)
Neoplastic nodule, multiple	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Pancreas	(49)	*(50)	(49)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Leukemia mononuclear	2 (4%)		
Acinus, adenoma	1 (2%)		1 (2%)
Pharynx	*(50)	*(50)	*(50)
Palate, papilloma squamous		1 (2%)	
Salivary glands	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Stomach	(49)	*(50)	(49)
Leukemia mononuclear	2 (4%)		1 (2%)
Forestomach, papilloma squamous	1 (2%)		2 (4%)
Tongue	*(50)	*(50)	*(50)
Mucosa, papilloma squamous			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	10 (20%)	1 (2%)	9 (18%)
Myocardium, leukemia mononuclear	1 (2%)		
Pericardium, leukemia mononuclear	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Bilateral, medulla, leukemia mononuclear	1 (2%)		
Bilateral, medulla, pheochromocytoma complex	1 (2%)		
Bilateral, medulla, pheochromocytoma benign	9 (18%)	2 (4%)	6 (12%)
Capsule, leukemia mononuclear	1 (2%)		
Cortex, adenoma	1 (2%)		
Cortex, leukemia mononuclear	1 (2%)		
Medulla, leukemia mononuclear	2 (4%)		
Medulla, pheochromocytoma benign	12 (24%)		12 (24%)
Islets, pancreatic	(49)	*(50)	(49)
Adenoma	1 (2%)		1 (2%)
Mixed tumor malignant	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
Parathyroid gland	(42)	*(50)	(44)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(49)	(44)	(49)
Leukemia mononuclear	1 (2%)	1 (2%)	
Pars distalis, adenoma	6 (12%)	10 (23%)	8 (16%)
Pars intermedia, carcinoma			1 (2%)
Thyroid gland	(49)	(49)	(50)
Bilateral, capsule, leukemia mononuclear	1 (2%)		
Bilateral, C-cell, adenoma		1 (2%)	1 (2%)
C-cell, adenoma	11 (22%)	7 (14%)	5 (10%)
C-cell, adenoma, multiple		1 (2%)	
Follicle, adenoma, cystic		2 (4%)	
Follicle, adenoma, cystic, papillary		1 (2%)	
GENERAL BODY SYSTEM			
Tissue, NOS	(2)	*(50)	(1)
Adenocarcinoma, metastatic, kidney	1 (50%)		
Chemodectoma benign			1 (100%)
Chemodectoma malignant	1 (50%)		
Organ of Zuckerkandl	1 (50%)		
Abdominal, liposarcoma		1 (2%)	
GENITAL SYSTEM			
Epididymis	(50)	*(50)	(50)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Leukemia mononuclear	1 (2%)		1 (2%)
Preputial gland	(43)	*(50)	(47)
Adenoma	2 (5%)	2 (4%)	7 (15%)
Carcinoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Prostate	(48)	*(50)	(50)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Leukemia mononuclear	1 (2%)		1 (2%)
Testes	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Bilateral, interstitial cell, adenoma	35 (70%)	25 (50%)	37 (74%)
Interstitial cell, adenoma	13 (26%)	12 (24%)	9 (18%)
HEMATOPOIETIC SYSTEM			
Blood	(26)	*(50)	(16)
Leukemia mononuclear	17 (65%)		12 (75%)
Bone marrow	(49)	*(50)	(50)
Leukemia mononuclear	12 (24%)		9 (18%)
Lymph node	(50)	*(50)	(50)
Carcinoma, metastatic, skin	1 (2%)		
Leukemia mononuclear	3 (6%)		1 (2%)
Axillary, leukemia mononuclear		1 (2%)	
Bronchial, leukemia mononuclear	1 (2%)		
Deep cervical, leukemia mononuclear	2 (4%)		
Lumbar, leukemia mononuclear			1 (2%)
Mandibular, leukemia mononuclear	29 (58%)	2 (4%)	16 (32%)
Mediastinal, leukemia mononuclear	17 (34%)		8 (16%)
Mesenteric, leukemia mononuclear	5 (10%)	4 (8%)	4 (8%)
Pancreatic, leukemia mononuclear			1 (2%)
Renal, leukemia mononuclear	2 (4%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	*(50)	(50)
Leukemia mononuclear	31 (62%)	12 (24%)	17 (34%)
Thymus	(39)	*(50)	(43)
Leukemia mononuclear	4 (10%)		5 (12%)
INTEGUMENTARY SYSTEM			
Mammary gland	(25)	*(50)	(22)
Adenocarcinoma	1 (4%)	1 (2%)	
Fibroadenoma	1 (4%)	3 (6%)	
Skin	(49)	*(50)	(50)
Basal cell adenoma		1 (2%)	
Carcinoma	1 (2%)		
Fibrosarcoma		1 (2%)	
Keratoacanthoma	1 (2%)		1 (2%)
Papilloma squamous	2 (4%)	1 (2%)	1 (2%)
Squamous cell carcinoma			2 (4%)
Trichoepithelioma		1 (2%)	1 (2%)
Abdominal, subcutaneous tissue, leukemia mononuclear	1 (2%)		
Axillary, subcutaneous tissue, leukemia mononuclear		1 (2%)	
Face, subcutaneous tissue, leukemia mononuclear	1 (2%)		
Sebaceous gland, adenocarcinoma		1 (2%)	
Subcutaneous tissue, fibroma	4 (8%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		2 (4%)	2 (4%)
Subcutaneous tissue, sarcoma	1 (2%)		
Subcutaneous tissue, schwannoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Carcinoma, metastatic, skin	1 (2%)		
Leukemia mononuclear	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Adenocarcinoma, metastatic, kidney	1 (2%)		
Adenocarcinoma, metastatic, mammary gland		1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)		
Carcinoma, metastatic, skin	1 (2%)		
Leukemia mononuclear	14 (28%)	1 (2%)	15 (30%)
Liposarcoma, metastatic, tissue, NOS		1 (2%)	
Sarcoma, metastatic	1 (2%)		
Interstitium, leukemia mononuclear	3 (6%)		
Interstitium, mediastinum, leukemia mononuclear	1 (2%)		
Mediastinum, leukemia mononuclear	3 (6%)		
Mediastinum, lipoma	1 (2%)		
Nose	(45)	(48)	(46)
Leukemia mononuclear	1 (2%)		
Turbinate, respiratory epithelium, adenocarcinoma		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Bilateral, leukemia mononuclear	1 (2%)		
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
Squamous cell carcinoma		1 (2%)	
URINARY SYSTEM			
Kidney	(50)	*(50)	(49)
Leukemia mononuclear	9 (18%)		1 (2%)
Mixed tumor malignant		1 (2%)	
Capsule, leukemia mononuclear	1 (2%)		
Renal tubule, adenocarcinoma	2 (4%)		
Urinary bladder	(48)	*(50)	(50)
Leukemia mononuclear	3 (6%)		1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	31 (62%)	17 (34%)	17 (34%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	12	16	12
Dead	5	9	6
Terminal sacrifice	33	25	32
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	49	48
Total primary neoplasms	152	102	119
Total animals with benign neoplasms	48	43	47
Total benign neoplasms	106	73	97
Total animals with malignant neoplasms	39	25	21
Total malignant neoplasms	45	28	22
Total animals with secondary neoplasms ***	3	2	
Total secondary neoplasms	12	2	
Total animals with neoplasms-- uncertain benign or malignant	1	1	
Total uncertain neoplasms	1	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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	06 0	07 2	07 9	08 2	08 9	09 4	09 4	09 4	09 5	09 5	09 6	09 6	09 7	09 8	09 8	10 0	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
CARCASS ID	05 3	06 1	06 2	06 5	07 3	07 5	08 3	08 2	09 2	09 5	10 1	10 4	10 4	11 1	11 1	11 6	11 1	11 3	11 5	12 1	12 3	12 4	12 5	13 1	13 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Colon, Peyer's patch, leukemia mononuclear													X												
Peyer's patch, rectum, leukemia mononuclear																	X								
Rectum, leukemia mononuclear													X												
Intestine small	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Leukemia mononuclear								X																	
Jejunum, sarcoma																									
Jejunum, Peyer's patch, leukemia mononuclear													X												
Peyer's patch, leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Hepatocellular carcinoma																							X		
Leukemia mononuclear	X	X		X	X	X	X	X		X	X		X			X	X		X			X		X	
Neoplastic nodule																									
Neoplastic nodule, multiple																							X		
Mesentery				+										+		+									
Adenocarcinoma, metastatic, kidney														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Leukemia mononuclear	X							X																	
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Stomach	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X						X																	
Forestomach, papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X				X										X	X								
Myocardium, leukemia mononuclear							X																		
Pericardium, leukemia mononuclear								X																	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Bilateral, medulla, leukemia mononuclear				X																					
Bilateral, medulla, pheochromocytoma complex																									
Bilateral, medulla, pheochromocytoma benign									X												X				X
Capsule, leukemia mononuclear								X																	
Cortex, adenoma																									
Cortex, leukemia mononuclear																	X								
Medulla, leukemia mononuclear						X	X																		
Medulla, pheochromocytoma benign										X			X			X	X						X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Mixed tumor malignant																									
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Pars distalis, adenoma										X		X												X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, capsule, leukemia mononuclear								X																	
C-cell, adenoma														X						X			X	X	
GENERAL BODY SYSTEM																									
Tissue, NOS														+											
Adenocarcinoma, metastatic, kidney														X											
Chemodectoma malignant																									
Organ of Zuckerkandl																									

\+ 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 RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL:
CARCASS ID	0035	0042	0043	0044	0051	0052	0062	0063	0065	0072	0073	0074	0075	0081	0082	0083	0084	0085	0091	0092	0093	0094	0095	0101	0104	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Colon, Peyer's patch, leukemia mononuclear								X	X																	3
Peyer's patch, rectum, leukemia mononuclear																										1
Rectum, leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma, metastatic, kidney																										1
Leukemia mononuclear																										1
Jejunum, sarcoma																X										1
Jejunum, Peyer's patch, leukemia mononuclear																X				X						3
Peyer's patch, leukemia mononuclear		X		X																						2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, kidney																										1
Hepatocellular carcinoma																			X		X					3
Leukemia mononuclear	X	X		X				X	X	X		X	X	X	X	X			X	X	X		X		X	31
Neoplastic nodule															X		X		X							3
Neoplastic nodule, multiple																										1
Mesentery						M																				3
Adenocarcinoma, metastatic, kidney																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, kidney																										1
Leukemia mononuclear																										2
Acinus, adenoma						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Forestomach, papilloma squamous																				X						1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X							X			X			X				X							10
Myocardium, leukemia mononuclear																										1
Pericardium, leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Bilateral, medulla, leukemia mononuclear																										1
Bilateral, medulla, pheochromocytoma complex																						X				1
Bilateral, medulla, pheochromocytoma benign			X							X		X						X	X	X						9
Capsule, leukemia mononuclear																										1
Cortex, adenoma			X																							1
Cortex, leukemia mononuclear																										1
Medulla, leukemia mononuclear																										2
Medulla, pheochromocytoma benign		X		X									X		X		X				X			X		12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X																									1
Mixed tumor malignant								X																		1
Parathyroid gland	I	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Adenoma																			X							1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Leukemia mononuclear																										1
Pars distalis, adenoma					X	X																				6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, capsule, leukemia mononuclear																										1
C-cell, adenoma						X				X					X	X					X		X	X		11
GENERAL BODY SYSTEM																										
Tissue, NOS		+																								2
Adenocarcinoma, metastatic, kidney																										1
Chemodectoma malignant		X																								1
Organ of Zuckerkandl		X																								1

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

WEEKS ON STUDY	06 0	07 2	07 9	08 2	08 9	09 4	09 4	09 4	09 5	09 5	09 6	09 6	09 7	09 8	09 8	10 0	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
CARCASS ID	05 3	01 1	03 2	04 5	01 3	05 5	03 3	02 2	10 2	10 5	01 2	05 4	01 4	04 1	07 1	06 4	06 1	01 3	01 5	02 1	02 3	02 4	02 5	03 1	03 4
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Leukemia mononuclear											X														
Preputial gland	M	–	M	M	+	+	+	+	+	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear								X																	
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Leukemia mononuclear								X																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Bilateral, interstitial cell, adenoma			X	X		X	X	X			X		X		X	X		X	X		X	X		X	
Interstitial cell, adenoma					X				X	X		X		X			X			X			X		X
HEMATOPOIETIC SYSTEM																									
Blood	–	+	M	–	–	+	+	+	–	+	–	–	+	+	+	+	+	+	+	–	+	–	–	–	
Leukemia mononuclear		X				X	X	X		X			X			X	X		X			X			
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X	X	X			X					X	X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin															X										
Leukemia mononuclear	X	X																							
Bronchial, leukemia mononuclear											X														
Deep cervical, leukemia mononuclear				X																					
Mandibular, leukemia mononuclear		X		X	X	X	X	X		X	X		X			X	X		X			X		X	
Mediastinal, leukemia mononuclear		X		X	X		X			X			X			X	X								
Mesenteric, leukemia mononuclear								X			X					X									
Renal, leukemia mononuclear											X					X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X	X	X	X	X		X	X		X			X	X		X			X		X	
Thymus	I	I	M	+	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X									X								
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	M	+	+	–	+	+	–	M	–	+	M	+	M	M	+	+	+	+	–	M	+
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma															X										
Keratoacanthoma							X																		
Papilloma squamous									X															X	
Abdominal, subcutaneous tissue, leukemia mononuclear								X																	
Face, subcutaneous tissue, leukemia mononuclear								X																	
Subcutaneous tissue, fibroma													X												
Subcutaneous tissue, sarcoma			X																						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin															X										
Leukemia mononuclear		X				X																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, kidney														X											
Alveolar/bronchiolar carcinoma																				X					
Carcinoma, metastatic, skin															X										
Leukemia mononuclear	X	X		X	X	X				X			X			X	X								
Sarcoma, metastatic			X																						
Interstitium, leukemia mononuclear							X	X																	
Interstitium, mediastinum, leukemia mononuclear											X														
Mediastinum, leukemia mononuclear								X																	
Mediastinum, lipoma				X																					
Nose	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye							+	M			+	+			I		+								
Harderian gland		+						+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, leukemia mononuclear								X																	
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X			X				X					X									
Capsule, leukemia mononuclear								X																	
Renal tubule, adenocarcinoma														X											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X				X																	

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL:
CARCASS ID	0035	0042	0043	0044	0051	0052	0062	0063	0065	0072	0073	0074	0075	0081	0082	0083	0084	0085	0091	0092	0093	0094	0095	0101	0104	TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, kidney																										1
Leukemia mononuclear																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma	X																			X						2
Leukemia mononuclear																										1
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, kidney																										1
Leukemia mononuclear																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X		X	X	X	X	X	35
Interstitial cell, adenoma									X	X	X									X						13
HEMATOPOIETIC SYSTEM																										
Blood	−	+	−	−	−	+	−	−	−	−	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	26
Leukemia mononuclear		X										X	X		X	X			X		X					17
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X							X			X								X						12
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, skin																										1
Leukemia mononuclear																				X						3
Bronchial, leukemia mononuclear																										1
Deep cervical, leukemia mononuclear												X														2
Mandibular, leukemia mononuclear	X	X		X				X	X	X		X	X	X	X	X			X		X		X		X	29
Mediastinal, leukemia mononuclear	X	X							X	X		X	X	X		X			X							17
Mesenteric, leukemia mononuclear												X			X											5
Renal, leukemia mononuclear																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X				X	X	X		X	X	X	X	X			X	X	X		X		X	31
Thymus	M	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	I	+	+	I	+	+	M	39
Leukemia mononuclear				X																						4
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	M	M	M	M	M	M	+	M	M	M	M	+	+	M	+	+	+	M	+	+	M	M	25
Adenocarcinoma										X																1
Fibroadenoma																		X								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Keratoacanthoma																										1
Papilloma squamous																										2
Abdominal, subcutaneous tissue, leukemia mononuclear																										1
Face, subcutaneous tissue, leukemia mononuclear																										1
Subcutaneous tissue, fibroma	X		X									X														4
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, skin																										1
Leukemia mononuclear																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, kidney																										1
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, skin																										1
Leukemia mononuclear									X			X	X		X				X							14
Sarcoma, metastatic																										1
Interstitium, leukemia mononuclear		X																								3
Interstitium, mediastinum, leukemia mononuclear																										1
Mediastinum, leukemia mononuclear	X	X																								3
Mediastinum, lipoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye						M																				4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Bilateral, leukemia mononuclear																										1
Zymbal gland						M					+															1
Carcinoma											X															1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X					X	X				X														9
Capsule, leukemia mononuclear																										1
Renal tubule, adenocarcinoma											X															2
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																			X							3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	060	061	067	069	074	080	081	083	085	089	090	091	092	095	096	097	097	098	099	100	100	100	102	102
CARCASS ID	351	382	374	321	331	403	325	362	323	333	332	341	384	322	364	312	373	372	315	393	353	381	392	383	334
ALIMENTARY SYSTEM																									
Intestine large								+																	
Intestine small															+										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear			X			X						X		X	X		X	X	X				X	X	
Mesentery								+																	
Pharynx							+																		
Palate, papilloma squamous							X																		
Stomach			+										+												
CARDIOVASCULAR SYSTEM																									
Heart																+			+						
Leukemia mononuclear																			X						
ENDOCRINE SYSTEM																									
Adrenal gland											+			+			+								
Bilateral, medulla, pheochromocytoma benign											X			X											
Parathyroid gland																									
Adenoma																									
Pituitary gland	+	+	I	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Pars distalis, adenoma	X														X							X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C cell, adenoma			X							X					X										
C cell, adenoma, multiple																									
Follicle, adenoma, cystic																									
Follicle, adenoma, cystic, papillary																					X				
GENERAL BODY SYSTEM																									
Tissue, NOS								+																	
Abdominal, liposarcoma								X																	
GENITAL SYSTEM																									
Epididymis																			+						
Preputial gland											+								+						
Adenoma																			X						
Carcinoma											X														
Prostate									+												+		+		
Seminal vesicle																					+				
Testes				+					+	+		+	+	+	+	+		+	+		+	+		+	+
Bilateral, interstitial cell, adenoma									X				X		X	X		X			X			X	X
Interstitial cell, adenoma				X						X		X		X								X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 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	31 1	31 1	31 1	32 4	33 5	34 2	34 3	34 4	34 5	35 2	35 1	35 5	36 1	36 3	36 5	37 1	37 5	38 5	39 1	39 4	39 5	40 1	40 2	40 4	40 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Intestine large																										1
Intestine small																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X														1
Leukemia mononuclear						X					X			X					X		X		X			16
Mesentery					+																					2
Pharynx																										1
Palate, papilloma squamous																										1
Stomach																										2
CARDIOVASCULAR SYSTEM																										
Heart																										2
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland																										3
Bilateral, medulla, pheochromocytoma benign																										2
Parathyroid gland						+																				1
Adenoma						X																				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		+	+	+		+	+	+	44
Leukemia mononuclear																										1
Pars distalis, adenoma				X	X	X						X		X										X		10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma														X												1
C-cell, adenoma	X								X		X												X			7
C cell, adenoma, multiple																								X		1
Follicle, adenoma, cystic																			X					X		2
Follicle, adenoma, cystic, papillary																										1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Abdominal, liposarcoma																										1
GENITAL SYSTEM																										
Epididymis																										1
Preputial gland											+															3
Adenoma											X															2
Carcinoma																										1
Prostate																										3
Seminal vesicle																										1
Testes	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X		X		X		X			X	X	X	X	X		X		25
Interstitial cell, adenoma										X		X		X		X	X						X		X	12

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

WEEKS ON STUDY	060	061	067	069	074	080	081	083	085	089	090	091	092	095	096	097	097	097	098	099	100	100	100	102	102
CARCASS ID	351	382	374	321	331	403	325	362	323	333	332	341	384	322	364	312	373	372	315	393	353	381	392	383	334
HEMATOPOIETIC SYSTEM																									
Lymph node			+			+					+			+	+			+		+	+				
Axillary, leukemia mononuclear						X																			
Mandibular, leukemia mononuclear			X															X							
Mesenteric, leukemia mononuclear			X			X								X	X										
Spleen			+			+						+		+	+		+	+	+				+	+	
Leukemia mononuclear			X			X						X		X	X		X	X	X				X	X	
Thymus																									
INTEGUMENTARY SYSTEM																									
Mammary gland												+		+						+					
Adenocarcinoma																				X					
Fibroadenoma												X		X											
Skin	+			+	+		+				+			+		+									
Basal cell adenoma																									
Fibrosarcoma											X														
Papilloma squamous																									
Trichoepithelioma																									
Axillary, subcutaneous tissue, leukemia mononuclear														X											
Sebaceous gland, adenocarcinoma																									
Subcutaneous tissue, fibroma	X															X									
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, schwannoma, NOS							X																		
MUSCULOSKELETAL SYSTEM																									
None																									
NERVOUS SYSTEM																									
Brain														+											
RESPIRATORY SYSTEM																									
Lung								+											+	+					
Adenocarcinoma, metastatic, mammary gland																				X					
Leukemia mononuclear																			X						
Liposarcoma, metastatic, tissue, NOS								X																	
Nose	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Turbinate, respiratory epithelium, adenocarcinoma																									
SPECIAL SENSES SYSTEM																									
Eye				+					+			+													
Zymbal gland		+																							
Squamous cell carcinoma		X																							
URINARY SYSTEM																									
Kidney													+						+	+	+	+			+
Mixed tumor malignant													X												
Urinary bladder								+		+															

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 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	31 3	31 4	32 4	33 5	34 2	34 3	34 4	34 5	35 2	35 4	35 5	36 1	36 3	36 5	37 1	37 5	38 5	39 1	39 4	39 5	40 1	40 2	40 4	40 5	38 2	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Lymph node													+													9
Axillary, leukemia mononuclear																										1
Mandibular, leukemia mononuclear																										2
Mesenteric, leukemia mononuclear																										4
Spleen		+									+							+				+				14
Leukemia mononuclear											X							X								12
Thymus											+															1
INTEGUMENTARY SYSTEM																										
Mammary gland																	+									4
Adenocarcinoma																										1
Fibroadenoma																	X									3
Skin	+					+							+	+						+						12
Basal cell adenoma														X												1
Fibrosarcoma																										1
Papilloma squamous													X													1
Trichoepithelioma	X																									1
Axillary, subcutaneous tissue, leukemia mononuclear																										1
Sebaceous gland, adenocarcinoma						X																				1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																				X						2
Subcutaneous tissue, schwannoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
None																										
NERVOUS SYSTEM																										
Brain																										1
RESPIRATORY SYSTEM																										
Lung																										3
Adenocarcinoma, metastatic, mammary gland																										1
Leukemia mononuclear																										1
Liposarcoma, metastatic, tissue, NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Turbinate, respiratory epithelium, adenocarcinoma				X																						1
SPECIAL SENSES SYSTEM																										
Eye								+																		4
Zymbal gland																										1
Squamous cell carcinoma																										1
URINARY SYSTEM																										
Kidney											+													+		8
Mixed tumor malignant																										1
Urinary bladder																										2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	0 3 2	0 6 5	0 7 5	0 8 6	0 8 8	0 8 9	0 9 0	0 9 1	0 9 3	0 9 4	0 9 5	0 9 5	0 9 7	0 9 8	0 9 8	0 9 8	0 9 9	1 0 0	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	6 0 3	5 8 1	5 7 3	5 4 5	5 8 2	5 9 3	5 4 4	5 2 4	5 7 4	5 5 5	5 5 1	5 1 4	5 5 4	5 4 3	5 2 2	5 5 2	5 2 5	5 9 1	5 1 1	5 1 1 2	5 1 3	5 1 5	5 2 1	5 2 3	5 3 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, Peyer's patch, leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X		X	X				X	X			X					X	X	
Neoplastic nodule																						X			
Mesentery														+											
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Forestomach, papilloma squamous		X																	X						
Tongue																									
Mucosa, papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X					X	X			X							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Bilateral, medulla, pheochromocytoma benign									X			X				X							X		
Medulla, pheochromocytoma benign		X			X						X		X					X	X						
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X						X				X						
Pars intermedia, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									X
C-cell, adenoma		X																							
GENERAL BODY SYSTEM																									
Tissue, NOS											+														
Chemodectoma benign											X														
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Penis				+																					
Preputial gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X			X	X		X		X		X	X			X	X	X	X	X	X		X	X	
Interstitial cell, adenoma			X		X		X		X		X				X							X			

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

WEEKS ON STUDY	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	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	TOTAL.
CARCASS ID	5 3 2	5 3 3	5 3 4	5 3 5	5 4 1	5 4 2	5 5 3	5 6 1	5 6 2	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 5	5 8 3	5 8 4	5 8 5	5 9 2	5 9 4	5 9 5	6 0 1	6 0 2	6 0 4	6 0 5	TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	47
Ileum, Peyer's patch, leukemia mononuclear												X														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X	X			X			X					X	X					17
Neoplastic nodule																										1
Mesentery																+										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma													X													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49
Leukemia mononuclear																										1
Forestomach, papilloma squamous																										2
Tongue															+											1
Mucosa, papilloma squamous															X											1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X	X			X								X						9
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									1
Bilateral, medulla, pheochromocytoma benign	X													X												6
Medulla, pheochromocytoma benign		X		X						X						X		X		X						12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	44
Adenoma		X																								1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X	X											X	X								8
Pars intermedia, carcinoma																								X		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma	X												X	X										X		5
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Chemodectoma benign																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Adenoma		X		X		X	X																		X	7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	37
Interstitial cell, adenoma					X					X																9

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

WEEKS ON STUDY	0 3 2	0 6 5	0 7 5	0 8 6	0 8 8	0 8 9	0 9 0	0 9 1	0 9 3	0 9 4	0 9 5	0 9 5	0 9 7	0 9 8	0 9 8	0 9 8	0 9 9	1 0 0	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	6 0 3	5 8 1	5 7 3	5 4 5	5 8 2	5 9 3	5 4 4	5 2 4	5 7 4	5 5 5	5 5 1	5 1 4	5 5 4	5 4 3	5 2 2	5 5 2	5 2 5	5 9 1	5 1 1	5 1 2	5 1 3	5 1 5	5 2 1	5 2 3	5 3 1
HEMATOPOIETIC SYSTEM																									
Blood		−	−	−	−	−	+	−	+	−	−	+	+	+	−	−	−	−	−	−	−	−	+	+	−
Leukemia mononuclear							X		X					X									X	X	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X		X	X				X	X			X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
Lumbar, leukemia mononuclear														X											
Mandibular, leukemia mononuclear						X	X		X	X				X	X			X					X	X	
Mediastinal, leukemia mononuclear						X			X	X				X				X					X		
Mesenteric, leukemia mononuclear						X			X					X				X							
Pancreatic, leukemia mononuclear														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X		X	X				X	X			X					X	X	
Thymus	+	+	M	+	+	+	M	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X			X									X							
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	M	M	+	+	+	M	M	M	M	M	M	M	M	M	+	M	M	+	+	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X			
Papilloma squamous																									
Squamous cell carcinoma								X										X							
Trichoepithelioma			X																						
Subcutaneous tissue, fibroma											X														
Subcutaneous tissue, fibrosarcoma													X				X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X		X	X				X	X			X					X		
Nose	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+														+								
Harderian gland		+				+	+	+					+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL.
CARCASS ID	53 2	53 3	53 4	53 5	54 1	54 2	55 3	56 1	56 2	56 3	56 4	56 5	57 1	57 2	57 5	58 3	58 4	58 5	59 2	59 4	59 5	60 1	60 2	60 4	60 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood	+	–	–	+	–	–	–	+	+	–		+	+	–	+	–	–	–	–	+	+	–	–	–	–	16
Leukemia mononuclear	X							X	X			X			X					X	X					12
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X														X											9
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lumbar, leukemia mononuclear																										1
Mandibular, leukemia mononuclear	X							X	X			X			X					X	X					16
Mediastinal, leukemia mononuclear	X																				X					8
Mesenteric, leukemia mononuclear																										4
Pancreatic, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X	X			X			X					X	X					17
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	M	+	+	+	+	+	+	+	+	43
Leukemia mononuclear	X																				X					5
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	M	+	M	M	+	+	+	M	+	M	M	+	+	M	+	M	M	+	M	M	+	22
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous								X																		1
Squamous cell carcinoma																										2
Trichoepithelioma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X	X			X			X					X	X					15
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+			+			36
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Control	5,000 ppm	10,000 ppm
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	21/50 (42%)	(b) 2/3 (67%)	18/50 (36%)
Adjusted Rates (c)	55 0%		43 9%
Terminal Rates (d)	16/33 (48%)		10/32 (31%)
Day of First Observation	663		454
Life Table Test (e)			P=0 398N
Logistic Regression Test (e)			P=0 364N
Fisher Exact Test (e)			P=0 341N
Adrenal Gland Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	22/50 (44%)	(b) 2/3 (67%)	18/50 (36%)
Adjusted Rates (c)	57 6%		43 9%
Terminal Rates (d)	17/33 (52%)		10/32 (31%)
Day of First Observation	663		454
Life Table Test (e)			P=0 329N
Logistic Regression Test (e)			P=0 292N
Fisher Exact Test (e)			P=0 270N
Preputial Gland: Adenoma			
Overall Rates (a)	2/43 (5%)	(b) 2/3 (67%)	7/47 (15%)
Adjusted Rates (c)	6 3%		21 6%
Terminal Rates (d)	2/32 (6%)		6/31 (19%)
Day of First Observation	727		681
Life Table Test (e)			P=0 074
Logistic Regression Test (e)			P=0 072
Fisher Exact Test (e)			P=0 101
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (c)	12 1%	0 0%	3 1%
Terminal Rates (d)	4/33 (12%)	0/25 (0%)	1/32 (3%)
Day of First Observation	727		727
Life Table Tests (e)	P=0 094N	P=0 102N	P=0 187N
Logistic Regression Tests (e)	P=0 094N	P=0 102N	P=0 187N
Cochran Armitage Trend Test (e)	P=0 082N		
Fisher Exact Test (e)		P=0 059N	P=0 181N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (c)	9 1%	4 0%	0 0%
Terminal Rates (d)	3/33 (9%)	1/25 (4%)	0/32 (0%)
Day of First Observation	727	727	
Life Table Tests (e)	P=0 071N	P=0 408N	P=0 126N
Logistic Regression Tests (e)	P=0 071N	P=0 408N	P=0 126N
Cochran Armitage Trend Test (e)	P=0 060N		
Fisher Exact Test (e)		P=0 309N	P=0 121N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (c)	15 2%	4 0%	3 1%
Terminal Rates (d)	5/33 (15%)	1/25 (4%)	1/32 (3%)
Day of First Observation	727	727	727
Life Table Tests (e)	P=0 057N	P=0 174N	P=0 108N
Logistic Regression Tests (e)	P=0 057N	P=0 174N	P=0 108N
Cochran Armitage Trend Test (e)	P=0 049N		
Fisher Exact Test (e)		P=0 102N	P=0 102N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	5,000 ppm	10,000 ppm
Mammary Gland: Fibroadenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (c)	3.0%	9.0%	0.0%
Terminal Rates (d)	1/33 (3%)	1/25 (4%)	0/32 (0%)
Day of First Observation	727	636	
Life Table Tests (e)	P=0.397N	P=0.240	P=0.506N
Logistic Regression Tests (e)	P=0.381N	P=0.294	P=0.506N
Cochran-Armitage Trend Test (e)	P=0.378N		
Fisher Exact Test (e)		P=0.309	P=0.500N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (c)	6.1%	11.9%	0.0%
Terminal Rates (d)	2/33 (6%)	1/25 (4%)	0/32 (0%)
Day of First Observation	727	636	
Life Table Tests (e)	P=0.244N	P=0.254	P=0.245N
Logistic Regression Tests (e)	P=0.228N	P=0.311	P=0.245N
Cochran-Armitage Trend Test (e)	P=0.222N		
Fisher Exact Test (e)		P=0.339	P=0.247N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	6/49 (12%)	10/44 (23%)	8/49 (16%)
Adjusted Rates (c)	16.9%	36.5%	21.6%
Terminal Rates (d)	4/32 (13%)	6/22 (27%)	5/32 (16%)
Day of First Observation	665	414	454
Life Table Tests (e)	P=0.345	P=0.072	P=0.384
Logistic Regression Tests (e)	P=0.341	P=0.133	P=0.386
Cochran-Armitage Trend Test (e)	P=0.343		
Fisher Exact Test (e)		P=0.144	P=0.387
Skin: Squamous Papilloma or Squamous Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (c)	5.3%	4.0%	8.2%
Terminal Rates (d)	1/33 (3%)	1/25 (4%)	1/32 (3%)
Day of First Observation	663	727	631
Life Table Tests (e)	P=0.388	P=0.579N	P=0.481
Logistic Regression Tests (e)	P=0.394	P=0.535N	P=0.500
Cochran-Armitage Trend Test (e)	P=0.399		
Fisher Exact Test (e)		P=0.500N	P=0.500
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	11.5%	4.8%	2.5%
Terminal Rates (d)	3/33 (9%)	0/25 (0%)	0/32 (0%)
Day of First Observation	674	414	659
Life Table Tests (e)	P=0.133N	P=0.417N	P=0.192N
Logistic Regression Tests (e)	P=0.104N	P=0.287N	P=0.184N
Cochran-Armitage Trend Test (e)	P=0.118N		
Fisher Exact Test (e)		P=0.339N	P=0.181N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (c)	11.5%	11.1%	7.9%
Terminal Rates (d)	3/33 (9%)	1/25 (4%)	0/32 (0%)
Day of First Observation	674	414	659
Life Table Tests (e)	P=0.441N	P=0.545	P=0.513N
Logistic Regression Tests (e)	P=0.410N	P=0.610N	P=0.506N
Cochran-Armitage Trend Test (e)	P=0.424N		
Fisher Exact Test (e)		P=0.643N	P=0.500N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	5,000 ppm	10,000 ppm
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (c)	13.3%	11.1%	7.9%
Terminal Rates (d)	3/33 (9%)	1/25 (4%)	0/32 (0%)
Day of First Observation	548	414	659
Life Table Tests (e)	P=0.313N	P=0.596N	P=0.374N
Logistic Regression Tests (e)	P=0.265N	P=0.426N	P=0.345N
Cochran-Armitage Trend Test (e)	P=0.290N		
Fisher Exact Test (e)		P=0.500N	P=0.357N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	48/50 (96%)	(b) 37/38 (97%)	46/50 (92%)
Adjusted Rates (c)	100.0%		97.9%
Terminal Rates (d)	33/33 (100%)		31/32 (97%)
Day of First Observation	548		454
Life Table Test (e)			P=0.531N
Logistic Regression Test (e)			P=0.427N
Fisher Exact Test (e)			P=0.339N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	11/49 (22%)	9/49 (18%)	6/50 (12%)
Adjusted Rates (c)	32.2%	30.5%	17.3%
Terminal Rates (d)	10/33 (30%)	6/24 (25%)	5/32 (16%)
Day of First Observation	680	469	454
Life Table Tests (e)	P=0.138N	P=0.527	P=0.154N
Logistic Regression Tests (e)	P=0.117N	P=0.497N	P=0.144N
Cochran-Armitage Trend Test (e)	P=0.108N		
Fisher Exact Test (e)		P=0.401N	P=0.133N
Thyroid Gland Follicle: Adenoma			
Overall Rates (a)	0/49 (0%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (c)	0.0%	11.5%	0.0%
Terminal Rates (d)	0/33 (0%)	2/24 (8%)	0/32 (0%)
Day of First Observation		700	
Life Table Tests (e)	P=0.625	P=0.080	(f)
Logistic Regression Tests (e)	P=0.630	P=0.088	(f)
Cochran-Armitage Trend Test (e)	P=0.634N		
Fisher Exact Test (e)		P=0.121	(f)
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	31/50 (62%)	(b,g) 17/50 (34%)	17/50 (34%)
Adjusted Rates (c)	68.2%	46.0%	41.2%
Terminal Rates (d)	19/33 (58%)	7/25 (28%)	9/32 (28%)
Day of First Observation	419	469	454
Life Table Tests (e)	P=0.017N	P=0.089N	P=0.021N
Logistic Regression Tests (e)	P=0.003N	P=0.005N	P=0.004N
Cochran-Armitage Trend Test (e)	P=0.003N		
Fisher Exact Test (e)		P=0.004N	P=0.004N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) 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).
(f) No P value is reported because no tumors were observed in the 10,000-ppm and control groups.
(g) Fourteen spleens were examined microscopically.

TABLE A4. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	19/50
N-Phenyl-2-naphthylamine	21/50
C.I. Disperse Yellow 3	13/50
D & C Red No. 9	10/50
C.I. Solvent Yellow 14	23/50
Rotenone	24/50
l-Ascorbic acid	17/50
TOTAL	127/350 (36.3%)
SD (b)	10.36%
Range (c)	
High	24/50
Low	10/50
Overall Historical Incidence	
TOTAL	636/1,936 (32.9%)
SD (b)	14.62%
Range (c)	
High	36/50
Low	5/50

(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 A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)		(50)
Submucosa, inflammation, chronic, multifocal			1 (2%)
Intestine large	(47)	(1)	(47)
Colon, Peyer's patch, hyperplasia, lymphoid, multifocal			3 (6%)
Colon, mesothelium, inflammation, chronic active, multifocal		1 (100%)	
Lamina propria, rectum, inflammation, subacute, multifocal		1 (100%)	
Peyer's patch, rectum, hyperplasia, lymphoid, multifocal			1 (2%)
Rectum, parasite metazoan	1 (2%)		
Rectum, mesothelium, inflammation, chronic active, multifocal		1 (100%)	
Intestine small	(47)	(1)	(47)
Necrosis		1 (100%)	
Jejunum, inflammation, proliferative, chronic active, multifocal		1 (100%)	
Jejunum, necrosis		1 (100%)	
Jejunum, lamina propria, metaplasia, osseous, multifocal		1 (100%)	
Jejunum, subserosa, diverticulum		1 (100%)	
Mucosa, necrosis		1 (100%)	
Liver	(50)	(50)	(50)
Angiectasis, focal	4 (8%)		
Angiectasis, multifocal	1 (2%)		
Basophilic focus	1 (2%)		3 (6%)
Basophilic focus, focal	1 (2%)		
Basophilic focus, multiple	14 (28%)	12 (24%)	11 (22%)
Basophilic focus, single	2 (4%)	2 (4%)	1 (2%)
Clear cell focus	1 (2%)		
Clear cell focus, focal			1 (2%)
Clear cell focus, multiple	1 (2%)	1 (2%)	4 (8%)
Clear cell focus, single		1 (2%)	3 (6%)
Eosinophilic focus			2 (4%)
Eosinophilic focus, multiple	3 (6%)		3 (6%)
Eosinophilic focus, single	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
Inflammation, granulomatous, multifocal	5 (10%)	7 (14%)	2 (4%)
Mixed cell focus	1 (2%)		
Bile duct, hyperplasia, chronic, multifocal	1 (2%)		
Bile duct, hyperplasia, cystic, multifocal			1 (2%)
Bile duct, hyperplasia, multifocal	35 (70%)	30 (60%)	23 (46%)
Bile duct, hyperplasia, nodular, multifocal	1 (2%)		
Capsule, hematocyst, single			1 (2%)
Centrilobular, necrosis, acute, multifocal			1 (2%)
Hepatocyte, cytoplasmic alteration, focal	1 (2%)		2 (4%)
Hepatocyte, cytoplasmic alteration, multifocal		2 (4%)	
Hepatocyte, degeneration, cystic, focal	10 (20%)	7 (14%)	6 (12%)
Hepatocyte, degeneration, cystic, multifocal	9 (18%)	5 (10%)	2 (4%)
Hepatocyte, necrosis, acute, multifocal			2 (4%)
Hepatocyte, necrosis, focal			1 (2%)
Hepatocyte, necrosis, multifocal			1 (2%)
Hepatocyte, necrosis, subacute, multifocal	1 (2%)		
Hepatocyte, vacuolization cytoplasmic, focal			1 (2%)
Hepatocyte, vacuolization cytoplasmic, multifocal	8 (16%)	8 (16%)	10 (20%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ALIMENTARY SYSTEM			
Liver (Continued)	(50)	(50)	(50)
Left lateral lobe, necrosis, acute, focal		1 (2%)	
Median lobe, hepatocyte, degeneration, fatty, multifocal			1 (2%)
Mesentery	(3)	(2)	(2)
Inflammation, granulomatous, multifocal		1 (50%)	
Necrosis, chronic, focal			1 (50%)
Fat, necrosis			1 (50%)
Fat, necrosis, acute, multifocal	1 (33%)		
Fat, necrosis, chronic, multifocal	1 (33%)		
Pancreas	(49)		(49)
Acinus, atrophy, focal	2 (4%)		7 (14%)
Acinus, atrophy, multifocal	27 (55%)		16 (33%)
Acinus, cytoplasmic alteration, focal	2 (4%)		
Acinus, cytoplasmic alteration, multifocal			1 (2%)
Artery, inflammation, chronic active, multifocal			1 (2%)
Duct, ectasia, focal	1 (2%)		
Duct, ectasia, multifocal	1 (2%)		1 (2%)
Salivary glands	(50)		(50)
Acinus, atrophy, focal	1 (2%)		
Acinus, atrophy, multifocal	1 (2%)		
Stomach	(49)	(2)	(49)
Forestomach, acanthosis, focal		1 (50%)	
Forestomach, acanthosis, multifocal	2 (4%)		
Forestomach, hyperkeratosis, focal		1 (50%)	
Forestomach, hyperkeratosis, multifocal	1 (2%)		
Forestomach, ulcer, subacute, focal	1 (2%)		
Forestomach, ulcer, subacute, multifocal	1 (2%)		
Forestomach, muscularis, inflammation, chronic, multifocal			1 (2%)
Forestomach, muscularis, mineralization, multifocal	1 (2%)		
Glandular, inflammation, chronic, multifocal			1 (2%)
Glandular, necrosis, acute, focal	1 (2%)		
Glandular, necrosis, acute, multifocal		2 (100%)	1 (2%)
Glandular, ulcer, acute, multifocal	1 (2%)		
Glandular, ulcer, subacute, focal	1 (2%)		
Muscularis, glandular, mineralization, multifocal	1 (2%)		
Submucosa, glandular, inflammation, subacute, multifocal	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	(2)	(50)
Artery, mineralization, multifocal	1 (2%)		
Atrium left, thrombus			1 (2%)
Atrium left, thrombus, chronic		1 (50%)	
Atrium left, thrombus, single	2 (4%)		
Atrium left, thrombus, subacute, multiple			1 (2%)
Myocardium, degeneration, chronic, multifocal	46 (92%)	2 (100%)	44 (88%)
Myocardium, degeneration, multifocal	1 (2%)		1 (2%)
Myocardium, inflammation, chronic, multifocal	1 (2%)		
Myocardium, mineralization, multifocal	1 (2%)		1 (2%)
Ventricle left, thrombus, chronic, focal	1 (2%)		
Ventricle left, thrombus, multiple			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(3)	(50)
Bilateral, cortex, hematopoietic cell proliferation, multifocal			1 (2%)
Bilateral, cortex, hyperplasia, multifocal	3 (6%)		
Bilateral, cortex, vacuolization cytoplasmic, multifocal	1 (2%)		1 (2%)
Bilateral, medulla, hyperplasia, multifocal	1 (2%)		
Cortex, congestion, multifocal			1 (2%)
Cortex, cytoplasmic alteration, focal	1 (2%)		2 (4%)
Cortex, degeneration, fatty, focal	5 (10%)	1 (33%)	6 (12%)
Cortex, degeneration, fatty, multifocal	5 (10%)		1 (2%)
Cortex, hematopoietic cell proliferation, multifocal	1 (2%)		
Cortex, hyperplasia, focal	6 (12%)		5 (10%)
Cortex, hyperplasia, multifocal	1 (2%)		1 (2%)
Cortex, karyomegaly, focal			1 (2%)
Cortex, necrosis, multifocal			1 (2%)
Cortex, nuclear alteration, focal	1 (2%)		
Cortex, vacuolization cytoplasmic, diffuse	1 (2%)		
Cortex, vacuolization cytoplasmic, multifocal	4 (8%)		
Medulla, cyst, single	1 (2%)		
Medulla, hyperplasia, focal	6 (12%)		10 (20%)
Medulla, hyperplasia, multifocal	6 (12%)		3 (6%)
Islets, pancreatic	(49)		(49)
Hyperplasia, focal			1 (2%)
Parathyroid gland	(42)	(1)	(44)
Cytoplasmic alteration, focal	1 (2%)		
Hyperplasia, diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)		
Hyperplasia, multifocal	2 (5%)		2 (5%)
Pituitary gland	(49)	(44)	(49)
Pars distalis, cyst	1 (2%)	4 (9%)	
Pars distalis, cyst, multiple		1 (2%)	1 (2%)
Pars distalis, hemorrhage, focal			1 (2%)
Pars distalis, hyperplasia, focal	7 (14%)	7 (16%)	5 (10%)
Pars distalis, hyperplasia, multifocal			5 (10%)
Pars distalis, karyomegaly, multifocal		1 (2%)	
Pars intermedia, cyst	2 (4%)		
Pars intermedia, cyst, multiple	2 (4%)		
Pars intermedia, hemorrhage, chronic, focal		1 (2%)	
Thyroid gland	(49)	(49)	(50)
Bilateral, follicle, cyst, multiple		1 (2%)	
C-cell, hyperplasia, focal	6 (12%)	4 (8%)	6 (12%)
C-cell, hyperplasia, multifocal	5 (10%)	5 (10%)	3 (6%)
Follicle, cyst	1 (2%)		5 (10%)
Follicle, cyst, multiple			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(1)	(50)
Bilateral, inflammation, chronic, multifocal			1 (2%)
Bilateral, inflammation, subacute, multifocal			1 (2%)
Head, granuloma sperm, single		1 (100%)	
Penis			(1)
Inflammation, necrotizing, acute, multifocal			1 (100%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Preputial gland	(43)	(3)	(47)
Abscess	1 (2%)		
Hyperplasia, glandular, focal	1 (2%)		
Hyperplasia, glandular, multifocal	1 (2%)		
Hyperplasia, nodular, squamous, multifocal			1 (2%)
Infiltration cellular, mononuclear cell, mononuclear cell, multifocal	1 (2%)		
Inflammation, chronic, multifocal	1 (2%)		
Inflammation, chronic active, multifocal	4 (9%)		3 (6%)
Inflammation, necrotizing, chronic active, multifocal			1 (2%)
Inflammation, subacute, multifocal	2 (5%)		
Bilateral, hyperplasia, glandular, multifocal	1 (2%)		
Bilateral, inflammation, chronic active, multifocal	27 (63%)		36 (77%)
Bilateral, duct, ectasia, focal	1 (2%)		1 (2%)
Bilateral, duct, ectasia, multifocal	6 (14%)		2 (4%)
Duct, ectasia, focal			3 (6%)
Duct, ectasia, multifocal	1 (2%)		1 (2%)
Right, duct, ectasia, diffuse	1 (2%)		
Prostate	(48)	(3)	(50)
Dilatation, multifocal		1 (33%)	
Inflammation, chronic, multifocal	6 (13%)		3 (6%)
Inflammation, chronic active, multifocal		2 (67%)	2 (4%)
Inflammation, granulomatous, multifocal	1 (2%)		
Inflammation, subacute, focal			1 (2%)
Inflammation, subacute, multifocal	2 (4%)		3 (6%)
Inflammation, suppurative, chronic, multifocal	2 (4%)		
Epithelium, hyperplasia, multifocal	1 (2%)		
Serosa, inflammation, chronic, multifocal			1 (2%)
Seminal vesicle		(1)	
Dilatation, multifocal		1 (100%)	
Testes	(50)	(38)	(50)
Atrophy, multifocal			1 (2%)
Bilateral, atrophy, multifocal	1 (2%)		
Bilateral, interstitial cell, hyperplasia, multifocal	2 (4%)		4 (8%)
Bilateral, seminiferous tubule, atrophy, chronic, multifocal			1 (2%)
Bilateral, seminiferous tubule, atrophy, multifocal	27 (54%)	20 (53%)	20 (40%)
Interstitial cell, hyperplasia, multifocal		4 (11%)	2 (4%)
Interstitial tissue, hemorrhage, chronic active, multifocal		1 (3%)	
Left, atrophy, multifocal		1 (3%)	
Left, interstitial cell, hyperplasia, focal			1 (2%)
Left, interstitial cell, hyperplasia, multifocal	5 (10%)	4 (11%)	2 (4%)
Left, seminiferous tubule, atrophy, multifocal	6 (12%)	3 (8%)	4 (8%)
Right, interstitial cell, hyperplasia, multifocal	8 (16%)	3 (8%)	3 (6%)
Right, interstitial tissue, hemorrhage, chronic active, multifocal		1 (3%)	
Right, seminiferous tubule, atrophy, multifocal	5 (10%)	4 (11%)	3 (6%)
Seminiferous tubule, atrophy, multifocal	4 (8%)	4 (11%)	3 (6%)
Vein, ectasia, chronic, multifocal		1 (3%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Blood	(26)		(16)
Neutrophilia	2 (8%)		
Bone marrow	(49)		(50)
Hyperplasia, neutrophil, multifocal	4 (8%)		1 (2%)
Myelofibrosis, multifocal	1 (2%)		
Myeloid cell, erythroid cell, hypoplasia, diffuse			1 (2%)
Myeloid cell, erythroid cell, hypoplasia, multifocal	2 (4%)		
Lymph node	(50)	(9)	(50)
Depletion lymphoid, multifocal			1 (2%)
Hyperplasia, lymphoid, multifocal	1 (2%)		
Inguinal, inflammation, granulomatous, multifocal		1 (11%)	
Lumbar, inflammation, granulomatous, multifocal		1 (11%)	
Mandibular, cyst	3 (6%)		1 (2%)
Mandibular, depletion lymphoid, multifocal			1 (2%)
Mandibular, hemorrhage, multifocal	3 (6%)		5 (10%)
Mandibular, hyperplasia, lymphoid, multifocal	6 (12%)		5 (10%)
Mandibular, hyperplasia, plasma cell, multifocal			5 (10%)
Mandibular, infiltration cellular, plasma cell, multifocal	1 (2%)		1 (2%)
Mandibular, inflammation, chronic, multifocal	1 (2%)		1 (2%)
Mandibular, inflammation, granulomatous, multifocal			1 (2%)
Mediastinal, hemorrhage, multifocal	3 (6%)		4 (8%)
Mediastinal, hyperplasia, lymphoid, multifocal	1 (2%)		
Mediastinal, inflammation, chronic, multifocal		1 (11%)	
Mediastinal, inflammation, chronic active, multifocal		1 (11%)	
Mediastinal, inflammation, granulomatous, multifocal	1 (2%)		3 (6%)
Mediastinal, inflammation, subacute, multifocal	1 (2%)		
Mediastinal, pigmentation, hemosiderin, multifocal		1 (11%)	
Mesenteric, cyst	1 (2%)		
Mesenteric, cyst, multiple	1 (2%)		1 (2%)
Mesenteric, hemorrhage, multifocal	1 (2%)	1 (11%)	
Mesenteric, hyperplasia, lymphoid, multifocal	1 (2%)		
Mesenteric, inflammation, chronic, multifocal	1 (2%)		
Mesenteric, inflammation, granulomatous, multifocal	1 (2%)	1 (11%)	
Pancreatic, cyst	1 (2%)		
Pancreatic, hemorrhage, multifocal	2 (4%)		
Spleen	(50)	(14)	(50)
Necrosis, subacute, diffuse	1 (2%)		
Capsule, cyst, multiple		1 (7%)	
Lymphoid follicle, necrosis, acute, multifocal			1 (2%)
Red pulp, fibrosis, chronic, focal		1 (7%)	
Red pulp, fibrosis, chronic, multifocal	1 (2%)	1 (7%)	
Red pulp, fibrosis, focal	2 (4%)	1 (7%)	
Red pulp, fibrosis, multifocal	3 (6%)	1 (7%)	1 (2%)
Red pulp, hematopoietic cell proliferation, multifocal	2 (4%)		5 (10%)
Red pulp, pigmentation, hemosiderin, multifocal	1 (2%)		2 (4%)
Thymus	(39)	(1)	(43)
Depletion lymphoid, multifocal	30 (77%)		33 (77%)
Artery, mediastinum, inflammation, proliferative, chronic, multifocal	1 (3%)		
Epithelial cell, hyperplasia, multifocal		1 (100%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Mammary gland	(25)	(4)	(22)
Acinus, hyperplasia, cystic, multifocal	19 (76%)		12 (55%)
Acinus, hyperplasia, multifocal	1 (4%)		2 (9%)
Skin	(49)	(12)	(50)
Abdominal, inflammation, suppurative, chronic, focal			1 (2%)
Abdominal, subcutaneous tissue, edema, subacute, multifocal			1 (2%)
Inguinal, abscess			1 (2%)
Inguinal, ulcer, chronic active, focal	1 (2%)		
Inguinal, subcutaneous tissue, inflammation, chronic active, multifocal			1 (2%)
Tail, hyperkeratosis, multifocal	1 (2%)		
Thoracic, subcutaneous tissue, hemorrhage, chronic active, diffuse		1 (8%)	
MUSCULOSKELETAL SYSTEM			
Bone	(49)		(48)
Femur, osteopetrosis, multifocal	3 (6%)		1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(1)	(50)
Cerebellum, hemorrhage, acute, multifocal	1 (2%)		
Cerebellum, cerebrum, hemorrhage, multifocal		1 (100%)	
Cerebrum, hemorrhage, acute, multifocal	1 (2%)		
Cerebrum, hemorrhage, focal	1 (2%)		
Medulla, cerebrum, hemorrhage, acute, multifocal			1 (2%)
Third ventricle, hemorrhage, focal			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(3)	(50)
Congestion, acute, diffuse			1 (2%)
Inflammation, granulomatous, multifocal	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia, multifocal	2 (4%)		
Bronchiole, epithelium, hyperplasia, multifocal	1 (2%)		
Interstitium, inflammation, acute, focal			2 (4%)
Interstitium, inflammation, chronic, focal		1 (33%)	
Interstitium, inflammation, chronic, multifocal	6 (12%)		1 (2%)
Interstitium, inflammation, subacute, multifocal			1 (2%)
Interstitium, metaplasia, osseous, focal	1 (2%)		
Interstitium, mineralization, multifocal	1 (2%)	1 (33%)	
Mediastinum, inflammation, granulomatous, multifocal			1 (2%)
Nose	(45)	(48)	(46)
Degeneration, multifocal			1 (2%)
Nasolacrimal duct, inflammation, chronic, multifocal	1 (2%)		
Nasolacrimal duct, inflammation, multifocal	1 (2%)		
Nasolacrimal duct, inflammation, subacute, focal	4 (9%)	1 (2%)	6 (13%)
Nasolacrimal duct, inflammation, subacute, multifocal	20 (44%)	19 (40%)	11 (24%)
Respiratory epithelium, degeneration, multifocal	25 (56%)	38 (79%)	42 (91%)
Respiratory epithelium, inflammation, chronic, focal	1 (2%)		
Respiratory epithelium, inflammation, subacute, multifocal	2 (4%)		
Respiratory epithelium, metaplasia, squamous, multifocal	2 (4%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Nose (Continued)	(45)	(48)	(46)
Submucosa, olfactory epithelium, inflammation, subacute, multifocal	1 (2%)		
Submucosa, respiratory epithelium, concretion, multifocal		1 (2%)	
Submucosa, respiratory epithelium, inflammation, acute, focal			1 (2%)
Submucosa, respiratory epithelium, inflammation, acute, multifocal	1 (2%)	3 (6%)	1 (2%)
Submucosa, respiratory epithelium, inflammation, chronic, multifocal	4 (9%)		
Submucosa, respiratory epithelium, inflammation, multifocal	1 (2%)		
Submucosa, respiratory epithelium, inflammation, subacute, focal		2 (4%)	1 (2%)
Submucosa, respiratory epithelium, inflammation, subacute, multifocal	19 (42%)	23 (48%)	22 (48%)
Submucosa, respiratory epithelium, inflammation, suppurative, chronic, multifocal			1 (2%)
Submucosa, respiratory epithelium, inflammation, suppurative, multifocal	2 (4%)		1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(4)	(2)
Cornea, inflammation, subacute, multifocal	1 (25%)		
Lens, cataract			1 (50%)
Lens, cataract, multifocal	2 (50%)	2 (50%)	
Retina, atrophy, multifocal	3 (75%)	2 (50%)	1 (50%)
Harderian gland	(43)		(36)
Hyperplasia, glandular, focal			1 (3%)
Hyperplasia, glandular, multifocal	1 (2%)		
Inflammation, granulomatous, multifocal			1 (3%)
Inflammation, subacute, multifocal			3 (8%)
URINARY SYSTEM			
Kidney	(50)	(8)	(49)
Congestion, multifocal		1 (13%)	
Cyst		1 (13%)	
Cyst, multiple	1 (2%)		
Polycystic kidney		1 (13%)	
Bilateral, nephropathy, chronic, multifocal	49 (98%)	6 (75%)	48 (98%)
Bilateral, cortex, cyst, multiple		1 (13%)	
Bilateral, cortex, mineralization, multifocal		1 (13%)	
Bilateral, pelvis, hydronephrosis, multifocal		1 (13%)	
Cortex, cyst	3 (6%)	1 (13%)	
Cortex, cyst, multiple	2 (4%)		
Cortex, cyst, single	4 (8%)		
Left, nephropathy, chronic, multifocal	1 (2%)		
Papilla, epithelium, hyperplasia, multifocal	1 (2%)		
Renal tubule, pigmentation, multifocal	1 (2%)		
Right, cyst		1 (13%)	
Urinary bladder	(48)	(2)	(50)
Inflammation, hemorrhagic, acute, multifocal		1 (50%)	
Mucosa, hyperplasia, multifocal	1 (2%)	1 (50%)	1 (2%)
Muscularis, inflammation, chronic active, multifocal		1 (50%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)	*(50)	(49)
Colon, Peyer's patch, leukemia mononuclear	1 (2%)		
Lamina propria, rectum, leukemia mononuclear	1 (2%)		
Intestine small	(48)	*(50)	(49)
Jejunum, Peyer's patch, leukemia mononuclear	2 (4%)		1 (2%)
Muscularis, jejunum, leiomyoma	1 (2%)		
Liver	(50)	*(50)	(50)
Leukemia mononuclear	11 (22%)	4 (8%)	11 (22%)
Neoplastic nodule		1 (2%)	
Pancreas	(50)	(48)	(49)
Leukemia mononuclear	1 (2%)		1 (2%)
Pharynx	*(50)	*(50)	*(50)
Palate, papilloma squamous			1 (2%)
Salivary glands	(50)	*(50)	(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Stomach	(49)	*(50)	(50)
Leukemia mononuclear	1 (2%)		
Glandular, leukemia mononuclear			1 (2%)
Glandular, lamina propria, leukemia mononuclear	1 (2%)		
Tongue	*(50)	*(50)	*(50)
Mucosa, papilloma squamous		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	5 (10%)		3 (6%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(49)
Bilateral, cortex, leukemia mononuclear		1 (2%)	
Bilateral, medulla, leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Bilateral, medulla, pheochromocytoma benign	1 (2%)		1 (2%)
Cortex, adenoma			1 (2%)
Cortex, carcinoma		1 (2%)	
Medulla, leukemia mononuclear	1 (2%)		
Medulla, pheochromocytoma benign	4 (8%)	3 (6%)	1 (2%)
Medulla, pheochromocytoma benign, multiple			1 (2%)
Islets, pancreatic	(50)	*(50)	(49)
Adenoma	1 (2%)		
Pituitary gland	(50)	(32)	(48)
Leukemia mononuclear			1 (2%)
Pars distalis, adenoma	29 (58%)	24 (75%)	22 (46%)
Pars distalis, adenoma, multiple	1 (2%)		1 (2%)
Pars distalis, carcinoma	2 (4%)	1 (3%)	5 (10%)
Pars distalis, leukemia mononuclear		1 (3%)	
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)		1 (2%)
Bilateral, C-cell, adenoma			1 (2%)
C-cell, adenoma	8 (16%)		6 (12%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma	3 (6%)		3 (6%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(38)	*(50)	(40)
Adenoma	5 (13%)	2 (4%)	3 (8%)
Leukemia mononuclear	1 (3%)		
Ovary	(50)	*(50)	(49)
Leukemia mononuclear	2 (4%)		2 (4%)
Uterus	(50)	*(50)	(50)
Adenoma	1 (2%)		
Leukemia mononuclear	1 (2%)		1 (2%)
Polyp stromal	11 (22%)	6 (12%)	10 (20%)
Sarcoma		1 (2%)	
Bilateral, polyp stromal	1 (2%)		1 (2%)
Cervix, sarcoma stromal	1 (2%)		
Endometrium, deciduoma, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	(12)	*(50)	(8)
Leukemia mononuclear	10 (83%)		5 (63%)
Bone marrow	(50)	*(50)	(49)
Leukemia mononuclear	5 (10%)		2 (4%)
Lymph node	(48)	(47)	(50)
Carcinoma, metastatic, skin			1 (2%)
Leukemia mononuclear		1 (2%)	
Axillary, leukemia mononuclear	1 (2%)		
Deep cervical, leukemia mononuclear	1 (2%)		
Mandibular, leukemia mononuclear	10 (21%)	2 (4%)	8 (16%)
Mediastinal, leukemia mononuclear	9 (19%)		3 (6%)
Mesenteric, leukemia mononuclear	3 (6%)	1 (2%)	1 (2%)
Pancreatic, leukemia mononuclear	1 (2%)		1 (2%)
Renal, leukemia mononuclear	1 (2%)		
Spleen	(50)	(48)	(50)
Leukemia mononuclear	11 (22%)	7 (15%)	11 (22%)
Thymus	(39)	*(50)	(47)
Carcinoma, metastatic, skin			1 (2%)
Leukemia mononuclear	4 (10%)		1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	*(50)	(46)
Adenocarcinoma	1 (2%)	1 (2%)	
Fibroadenoma	8 (17%)	7 (14%)	3 (7%)
Fibroadenoma, multiple	1 (2%)	1 (2%)	1 (2%)
Leukemia mononuclear	1 (2%)		
Skin	(50)	*(50)	(50)
Basosquamous tumor benign			1 (2%)
Papilloma squamous	1 (2%)		
Trichoepithelioma			1 (2%)
Subcutaneous tissue, carcinoma			1 (2%)
Subcutaneous tissue, fibroma		1 (2%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		
Thoracic, subcutaneous tissue, lipoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(49)	*(50)	(50)
Lumbar, osteosarcoma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	*(50)	(48)
Carcinoma, metastatic, pituitary gland	1 (2%)		2 (4%)
Leukemia mononuclear	1 (2%)		1 (2%)
Cerebrum, granular cell tumor benign			1 (2%)
Media, astrocytoma malignant			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Carcinoma, metastatic, skin			1 (2%)
Carcinoma, metastatic, thyroid gland	1 (2%)		1 (2%)
Leukemia mononuclear	10 (20%)		5 (10%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma		1 (2%)	
URINARY SYSTEM			
Kidney	(50)	*(50)	(49)
Leukemia mononuclear	2 (4%)		1 (2%)
Renal tubule, adenoma	1 (2%)		
Urinary bladder	(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)		
Transitional epithelium, papilloma			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	11 (22%)	7 (14%)	11 (22%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	34	43	40
Moribund	14	3	8
Dead	2	4	2
TUMOR SUMMARY			
Total animals with primary neoplasms **	47	36	44
Total primary neoplasms	95	58	83
Total animals with benign neoplasms	43	33	37
Total benign neoplasms	75	46	61
Total animals with malignant neoplasms	17	12	20
Total malignant neoplasms	19	12	22
Total animals with secondary neoplasms ***	2		4
Total secondary neoplasms	2		6
Total animals with neoplasms uncertain benign or malignant	1		
Total uncertain neoplasms	1		

* 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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	042	062	080	083	088	091	095	099	099	099	099	100	101	102	102	104	105	105	105	105	105	105	105	105	105
CARCASS ID	193	161	172	191	233	633	522	822	811	944	204	333	544	433	455	205	111	112	113	114	115	121	222	244	255
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Colon, Peyer's patch, leukemia mononuclear									X																
Lamina propria, rectum, leukemia mononuclear									X																
Intestine small	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Jejunum, Peyer's patch, leukemia mononuclear													X												
Muscularis, jejunum, leiomyoma										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X				X	X	X		X					X			
Mesentery			+								+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Glandular, lamina propria, leukemia mononuclear									X																
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X				X	X	X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, medulla, leukemia mononuclear													X	X											
Bilateral, medulla, pheochromocytoma benign																									
Medulla, leukemia mononuclear															X										
Medulla, pheochromocytoma benign								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	+	M	M	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X	X		X	X	X	X	X			X	X	X			X				X
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
C-cell, adenoma												X							X						X
C-cell, adenoma, multiple														X											
C-cell, carcinoma								X																	
GENERAL BODY SYSTEM																									
Tissue, NOS					+																				

+ 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 RATS: UNTREATED CONTROL (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	
CARCASS ID	131	132	134	135	141	142	144	151	153	155	162	164	165	171	173	174	175	183	184	185	192	195	201	202	203	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Colon, Peyer's patch, leukemia mononuclear																										1
Lamina propria, rectum, leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Jejunum, Peyer's patch, leukemia mononuclear																			X							2
Muscularis, jejunum, leiomyoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																		X		X					11
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																			X							1
Glandular, lamina propria, leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							5
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, medulla, leukemia mononuclear																										2
Bilateral, medulla, pheochromocytoma benign																					X					1
Medulla, leukemia mononuclear																										1
Medulla, pheochromocytoma benign				X									X							X						4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	M	+	+	+	M	+	+	M	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X	X	X			X	X	X				X		X	X		X	X	X	X	29
Pars distalis, adenoma, multiple										X																1
Pars distalis, carcinoma														X	X											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							1
C-cell, adenoma		X								X	X											X			X	8
C-cell, adenoma, multiple																										1
C-cell, carcinoma						X								X												3
GENERAL BODY SYSTEM																										
Tissue, NOS																										1

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

WEEKS ON STUDY	0 4 2	0 6 2	0 8 0	0 8 3	0 8 8	0 9 1	0 9 5	0 9 9	0 9 9	0 9 9	0 9 9	1 0 0	1 0 1	1 0 2	1 0 2	1 0 4	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
CARCASS ID	1 9 3	1 6 1	1 7 2	1 9 1	1 2 3	1 6 3	1 5 2	1 8 2	1 8 1	1 9 4	2 0 4	1 3 3	1 5 4	1 4 3	1 4 5	2 0 5	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 2 1	1 2 2	1 2 4	1 2 5
GENITAL SYSTEM																									
Clitoral gland	M	M	M	M	M	M	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Leukemia mononuclear																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Leukemia mononuclear																									
Polyp stromal																		X	X			X	X		
Bilateral, polyp stromal																								X	
Cervix, sarcoma stromal		X																							
Endometrium, deciduoma, NOS																	X								
HEMATOPOIETIC SYSTEM																									
Blood	–	+	–	–	–	+	–	+	+	–	–	–	+	+	+	–	–	–	–	–	–	+	–	–	–
Leukemia mononuclear						X		X	X				X	X	X							X			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X				X	X											
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, leukemia mononuclear																									
Deep cervical, leukemia mononuclear																						X			
Mandibular, leukemia mononuclear						X		X	X				X	X	X		X					X			
Mediastinal, leukemia mononuclear						X		X	X				X	X			X					X			
Mesenteric, leukemia mononuclear													X	X											
Pancreatic, leukemia mononuclear														X											
Renal, leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X				X	X	X		X					X			
Thymus	+	+	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X									X			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
Fibroadenoma					X	X		X	X	X															
Fibroadenoma, multiple							X																		
Leukemia mononuclear																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma	X																								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Leukemia mononuclear														X											
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear						X		X	X				X	X	X		X					X			
Nose	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye													+		+		+								
Harderian gland				M		+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (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	
CARCASS ID	1331	1332	1334	1335	1341	1342	1344	1351	1353	1355	1362	1364	1365	1371	1373	1374	1375	1383	1384	1385	1392	1395	2001	2002	2003	TOTAL TISSUES TUMORS
GENITAL SYSTEM																										
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	M	+	38
Adenoma											X				X							X			X	5
Leukemia mononuclear																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																			X							1
Polyp stromal	X			X											X		X	X	X			X			X	11
Bilateral, polyp stromal																										1
Cervix, sarcoma stromal																										1
Endometrium, deciduoma, NOS																										1
HEMATOPOIETIC SYSTEM																										
Blood	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	12
Leukemia mononuclear	X																		X		X					10
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Axillary, leukemia mononuclear																			X							1
Deep cervical, leukemia mononuclear																										1
Mandibular, leukemia mononuclear	X																		X							10
Mediastinal, leukemia mononuclear	X																		X							9
Mesenteric, leukemia mononuclear																			X							3
Pancreatic, leukemia mononuclear																										1
Renal, leukemia mononuclear																			X							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																		X		X					11
Thymus	+	M	+	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	M	+	+	+	+	39
Leukemia mononuclear																			X							4
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	46
Adenocarcinoma																										1
Fibroadenoma					X			X					X													8
Fibroadenoma, multiple																										1
Leukemia mononuclear																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous				X																						1
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland														X												1
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland						X																				1
Leukemia mononuclear	X																		X							10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Eye			+																							4
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		+	+	+	+		+	+	+	40
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							2
Renal tubule, adenoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	027	081	084	088	093	097	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	231	293	271	214	241	264	303	211	212	213	215	221	222	223	224	225	232	233	234	235	242	243	244	245	251
ALIMENTARY SYSTEM																									
Liver			+			+	+	+	+			+		+	+			+		+	+			+	+
Leukemia mononuclear			X			X																			
Neoplastic nodule												X													
Mesentery			M																						
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Tongue																									+
Mucosa, papilloma squamous																									X
CARDIOVASCULAR SYSTEM																									
None																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, cortex, leukemia mononuclear			X																						
Bilateral, medulla, leukemia mononuclear						X																			
Cortex, carcinoma																		X							
Medulla, pheochromocytoma benign											X														
Islets, pancreatic																									
Pituitary gland			+	+	+		+	+	+			+	+			+	+				+	+	+	+	+
Pars distalis, adenoma					X			X	X			X	X			X					X	X	X	X	X
Pars distalis, carcinoma							X																		
Pars distalis, leukemia mononuclear			X																						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland																		+							
Adenoma																		X							
Ovary																+									
Uterus		+	+			+			+						+					+			+		
Polyp stromal			X			X			X						X										
Sarcoma		X																							
HEMATOPOIETIC SYSTEM																									
Lymph node	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mandibular, leukemia mononuclear			X			X																			
Mesenteric, leukemia mononuclear						X																			
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X					X												X		
INTEGUMENTARY SYSTEM																									
Mammary gland								+																	
Adenocarcinoma																									
Fibroadenoma								X																	
Fibroadenoma, multiple																									
Skin									+																
Subcutaneous tissue, fibroma									X																
MUSCULOSKELETAL SYSTEM																									
None																									
NERVOUS SYSTEM																									
None																									
RESPIRATORY SYSTEM																									
Lung					+																				
SPECIAL SENSES SYSTEM																									
Eye			A																						
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney																									
Urinary bladder	+																								

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 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	
CARCASS ID	2552	2553	2554	2555	2561	2562	2563	2565	2572	2573	2574	2575	2581	2582	2583	2584	2585	2591	2592	2594	2595	3001	3002	3004	3005	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Liver					+					+	+	+		+			+			+	+	+		+		23
Leukemia mononuclear										X												X				4
Neoplastic nodule																										1
Mesentery																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Mucosa, papilloma squamous																										1
CARDIOVASCULAR SYSTEM																										
None																										
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, cortex, leukemia mononuclear																										1
Bilateral, medulla, leukemia mononuclear																						X				2
Cortex, carcinoma																										1
Medulla, pheochromocytoma benign							X																X			3
Islets, pancreatic														+											+	2
Pituitary gland	+		+	+	+	+		+	+	+			+		+	+	+		+		+	+	+		+	32
Pars distalis, adenoma	X		X		X	X			X	X			X		X	X	X		X			X			X	24
Pars distalis, carcinoma																										1
Pars distalis, leukemia mononuclear																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																									+	2
Adenoma																									X	2
Ovary			+					+							+									+		5
Uterus	+						+									+										10
Polyp stromal	X															X										6
Sarcoma																										1
HEMATOPOIETIC SYSTEM																										
Lymph node	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																						X				1
Mandibular, leukemia mononuclear																										2
Mesenteric, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear						X				X												X				7
INTEGUMENTARY SYSTEM																										
Mammary gland			+			+						+	+		+					+			+		+	9
Adenocarcinoma																									X	1
Fibroadenoma			X			X						X	X		X								X			7
Fibroadenoma, multiple																				X						1
Skin																			+							2
Subcutaneous tissue, fibroma																										1
MUSCULOSKELETAL SYSTEM																										
None																										
NERVOUS SYSTEM																										
None																										
RESPIRATORY SYSTEM																										
Lung																										1
SPECIAL SENSES SYSTEM																										
Eye																				+						1
Zymbal gland																		+								1
Carcinoma																		X								1
URINARY SYSTEM																										
Kidney																	+									1
Urinary bladder																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	04 49	04 49	06 01	06 07	07 09	08 02	09 02	09 06	09 07	10 02	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
CARCASS ID	43 02	50 44	43 05	49 33	45 35	42 55	44 33	48 32	46 05	44 02	41 11	41 12	41 13	41 14	41 15	42 21	42 22	42 23	42 24	43 11	43 33	43 34	44 11	44 45
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Jejunum, Peyer's patch, leukemia mononuclear		X																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X					X				X			X						X		X
Mesentery											+													
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X															
Pharynx																								
Palate, papilloma squamous																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X															
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glandular, leukemia mononuclear	X																							
Tooth																								
CARDIOVASCULAR SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X					X															
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	
Bilateral, medulla, leukemia mononuclear									X															
Bilateral, *medulla, pheochromocytoma* benign	X																							
Cortex, adenoma																								
Medulla, pheochromocytoma benign																		X						
Medulla, pheochromocytoma benign, multiple																								
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	I	+	+	+	A	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	I	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X															
Pars distalis, adenoma					X			X		X	X	X	X			X		X						X
Pars distalis, adenoma, multiple																				X				
Pars distalis, carcinoma																					X	X		
Pars intermedia, adenoma													X											
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X															
Bilateral, C-cell, adenoma																					X			
C-*cell, adenoma*		X																				X		
C-cell, carcinoma								X				X	X											
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Clitoral gland	+	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																	X							
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X								X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X															
Polyp stromal			X			X									X			X						
Bilateral, polyp stromal	X																							

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL
CARCASS ID	45 1	45 2	45 3	45 4	46 1	46 2	46 3	46 4	47 1	47 2	47 3	47 4	47 5	48 1	48 3	48 4	48 5	49 1	49 2	49 4	49 5	50 1	50 2	50 3	50 5	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Jejunum, Peyer's patch, leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X			X													X			11
Mesentery											+															2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Pharynx						+																				1
Palate, papilloma squamous						X																				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glandular, leukemia mononuclear																										1
Tooth							+																			1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, medulla, leukemia mononuclear																										1
Bilateral, medulla, pheochromocytoma benign																										1
Cortex, adenoma																						X				1
Medulla, pheochromocytoma benign																										1
Medulla, pheochromocytoma benign, multiple																	X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Pars distalis, adenoma		X				X	X	X	X		X	X			X		X	X	X			X	X	X		22
Pars distalis, adenoma, multiple																										1
Pars distalis, carcinoma					X									X					X							5
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Bilateral, C-cell, adenoma																										1
C-cell, adenoma							X		X							X						X				6
C-cell, carcinoma																										3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	M	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	40
Adenoma								X																X		3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Polyp stromal		X		X	X				X										X	X						10
Bilateral, polyp stromal																										1

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

WEEKS ON STUDY	049	049	061	067	079	082	092	096	097	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	43202	50204	43505	43903	45505	42505	44403	48202	46505	44202	41101	41102	41103	41104	41105	41201	42202	42203	42204	43101	43303	43404	44401	44404	44505
HEMATOPOIETIC SYSTEM																									
Blood	−	−	−	+	−	−	+	-	+	−	−	−	−	−	−	−	+	−	-	-	−	−	+	−	+
Leukemia mononuclear				X					X														X		X
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X								X																
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin							X																		
Mandibular, leukemia mononuclear	X	X		X					X														X		X
Mediastinal, leukemia mononuclear	X								X														X		
Mesenteric, leukemia mononuclear									X																
Pancreatic, leukemia mononuclear				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X					X					X			X						X		X
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Carcinoma, metastatic, skin							X																		
Leukemia mononuclear									X																
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma					X																				
Fibroadenoma, multiple											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Trichoepithelioma																	X								
Subcutaneous tissue, carcinoma							X																		
Subcutaneous tissue, fibroma		X	X																						
Thoracic, subcutaneous tissue, lipoma																			X						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, osteosarcoma								X																	
Skeletal muscle																			+						
NERVOUS SYSTEM																									
Brain	+	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Carcinoma, metastatic, pituitary gland																						X			
Leukemia mononuclear	X																								
Cerebrum, granular cell tumor benign																									
Media, astrocytoma malignant								X																	
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland												X													
Carcinoma, metastatic, skin							X																		
Leukemia mononuclear	X			X					X																X
Nose	+	+	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
SPECIAL SENSES SYSTEM																									
Eye	+													+											
Harderian gland		+						+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																	X								

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL
CARCASS ID	45 1	45 2	45 3	45 4	46 1	46 2	46 3	46 4	47 1	47 2	47 3	47 4	47 5	48 1	48 3	48 4	48 5	49 1	49 2	49 4	49 5	50 1	50 2	50 3	50 5	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood		–	–		–			–	–	+	–		–	–	–	–	–	+	–	–	–	–	–	–	–	8
Leukemia mononuclear										X																5
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic skin																										1
Mandibular, leukemia mononuclear										X													X			8
Mediastinal, leukemia mononuclear																										3
Mesenteric leukemia mononuclear																										1
Pancreatic, leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X			X													X			11
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, skin																										1
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma					X			X																		3
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign																								X		1
Trichoepithelioma																										1
Subcutaneous tissue, carcinoma																										1
Subcutaneous tissue, fibroma																										2
Thoracic, subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumbar, osteosarcoma																										1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic pituitary gland					X																					2
Leukemia mononuclear																										1
Cerebrum granular cell tumor benign															X											1
Media, astrocytoma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Carcinoma, metastatic, skin																										1
Leukemia mononuclear										X																5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye		+																			+					4
Harderian gland		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma																										1

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Control	2,500 ppm	5,000 ppm
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	3/49 (6%)	3/49 (6%)
Adjusted Rates (b)	13 8%	7 0%	7 0%
Terminal Rates (c)	4/34 (12%)	3/43 (7%)	2/39 (5%)
Day of First Observation	692	728	343
Life Table Tests (d)	P=0 232N	P=0.250N	P=0.306N
Logistic Regression Tests (d)	P=0 289N	P=0.310N	P=0.357N
Cochran-Armitage Trend Test (d)	P=0 292N		
Fisher Exact Test (d)		P=0.369N	P=0.369N
Clitoral Gland: Adenoma			
Overall Rates (a)	5/38 (13%)	(e) 2/2 (100%)	3/40 (7%)
Adjusted Rates (b)	16.1%		8.3%
Terminal Rates (c)	5/31 (16%)		3/36 (8%)
Day of First Observation	728		728
Life Table Test (d)			P=0.275N
Logistic Regression Test (d)			P=0.275N
Fisher Exact Test (d)			P=0.327N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	9/50 (18%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	20.7%	18.6%	9.5%
Terminal Rates (c)	3/34 (9%)	8/43 (19%)	3/40 (7%)
Day of First Observation	610	728	548
Life Table Tests (d)	P=0.072N	P=0.363N	P=0.108N
Logistic Regression Tests (d)	P=0.098N	P=0.494N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.097N		
Fisher Exact Test (d)		P=0.500N	P=0.117N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	20.7%	20.9%	9.5%
Terminal Rates (c)	3/34 (9%)	9/43 (21%)	3/40 (7%)
Day of First Observation	610	728	548
Life Table Tests (d)	P=0.074N	P=0.451N	P=0.108N
Logistic Regression Tests (d)	P=0 103N	P=0.595N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test (d)		P=0.602N	P=0.117N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	30/50 (60%)	(e) 24/32 (75%)	23/48 (48%)
Adjusted Rates (b)	67.8%		53.4%
Terminal Rates (c)	20/34 (59%)		20/40 (50%)
Day of First Observation	580		548
Life Table Test (d)			P=0.049N
Logistic Regression Test (d)			P=0.150N
Fisher Exact Test (d)			P=0.159N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	2/50 (4%)	(e) 1/32 (3%)	5/48 (10%)
Adjusted Rates (b)	5.9%		12.5%
Terminal Rates (c)	2/34 (6%)		5/40 (13%)
Day of First Observation	728		728
Life Table Test (d)			P=0.285
Logistic Regression Test (d)			P=0.285
Fisher Exact Test (d)			P=0.201

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	2,500 ppm	5,000 ppm
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	32/50 (64%)	(e) 25/32 (78%)	28/48 (58%)
Adjusted Rates (b)	72.4%		65.0%
Terminal Rates (c)	22/34 (65%)		25/40 (63%)
Day of First Observation	580		548
Life Table Test (d)			P=0.106N
Logistic Regression Test (d)			P=0.342N
Fisher Exact Test (d)			P=0.356N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/50 (18%)	(f)	7/49 (14%)
Adjusted Rates (b)	24.7%		16.7%
Terminal Rates (c)	7/34 (21%)		6/40 (15%)
Day of First Observation	695		343
Life Table Test (d)			P=0.282N
Logistic Regression Test (d)			P=0.412N
Fisher Exact Test (d)			P=0.410N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	(f)	3/49 (6%)
Adjusted Rates (b)	8.1%		7.2%
Terminal Rates (c)	2/34 (6%)		2/40 (5%)
Day of First Observation	692		671
Life Table Test (d)			P=0.614N
Logistic Regression Test (d)			P=0.654
Fisher Exact Test (d)			P=0.651
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	(f)	10/49 (20%)
Adjusted Rates (b)	31.9%		23.4%
Terminal Rates (c)	9/34 (26%)		8/40 (20%)
Day of First Observation	692		343
Life Table Test (d)			P=0.284N
Logistic Regression Test (d)			P=0.429N
Fisher Exact Test (d)			P=0.426N
Uterus: Stromal Polyp			
Overall Rates (a)	12/50 (24%)	(e) 6/10 (60%)	11/50 (22%)
Adjusted Rates (b)	35.3%		24.9%
Terminal Rates (c)	12/34 (35%)		8/40 (20%)
Day of First Observation	728		343
Life Table Test (d)			P=0.352N
Logistic Regression Test (d)			P=0.498N
Fisher Exact Test (d)			P=0.500N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (a)	11/50 (22%)	(e,g) 7/50 (14%)	11/50 (22%)
Adjusted Rates (b)	26.8%	15.4%	24.3%
Terminal Rates (c)	5/34 (15%)	5/43 (12%)	7/40 (18%)
Day of First Observation	636	584	343
Life Table Tests (d)	P=0.460N	P=0.134N	P=0.493N
Logistic Regression Tests (d)	P=0.392	P=0.213N	P=0.572N
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Test (d)		P=0.218N	P=0.595N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (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) No tissues were examined microscopically for the 2,500-ppm group.
(g) Twenty-three livers were examined microscopically.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)		(49)
Colon, parasite metazoan, single			1 (2%)
Rectum, parasite metazoan	2 (4%)		
Rectum, parasite metazoan, multifocal	1 (2%)		
Rectum, parasite metazoan, single			2 (4%)
Intestine small	(48)		(49)
Ileum, Peyer's patch, hyperplasia, lymphoid, multifocal			1 (2%)
Liver	(50)	(23)	(50)
Angiectasis, focal	1 (2%)		
Angiectasis, multifocal		1 (4%)	1 (2%)
Basophilic focus, multiple	33 (66%)	14 (61%)	42 (84%)
Basophilic focus, single	2 (4%)	2 (9%)	1 (2%)
Clear cell focus		2 (9%)	
Clear cell focus, multiple			1 (2%)
Clear cell focus, single	2 (4%)		3 (6%)
Cyst		1 (4%)	
Hemorrhage, acute, multifocal	1 (2%)		
Hyperplasia, focal			1 (2%)
Inflammation, granulomatous, focal		2 (9%)	
Inflammation, granulomatous, multifocal	26 (52%)	7 (30%)	22 (44%)
Inflammation, subacute, multifocal		2 (9%)	
Inflammation, membranoproliferative, focal			1 (2%)
Bile duct, hyperplasia, multifocal	8 (16%)	2 (9%)	7 (14%)
Centrilobular, pigmentation, hemosiderin, multifocal			1 (2%)
Hepatocyte, degeneration, cystic, focal	1 (2%)	3 (13%)	
Hepatocyte, necrosis, acute, multifocal	3 (6%)		1 (2%)
Hepatocyte, necrosis, multifocal			2 (4%)
Hepatocyte, vacuolization cytoplasmic, multifocal	9 (18%)		6 (12%)
Hepatocyte, centrilobular, necrosis, subacute, multifocal			1 (2%)
Left lateral lobe, angiectasis, focal			1 (2%)
Median lobe, atrophy, chronic, multifocal			1 (2%)
Periportal, hematopoietic cell proliferation, multifocal	2 (4%)		
Periportal, infiltration cellular, lymphocytic, acute, multifocal			1 (2%)
Sinusoid, subserosa, congestion, acute, multifocal			1 (2%)
Mesentery	(2)		(2)
Inflammation, chronic, multifocal	1 (50%)		
Inflammation, granulomatous, focal	1 (50%)		
Inflammation, granulomatous, multifocal			1 (50%)
Pancreas	(50)	(48)	(49)
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Acinus, atrophy, focal	5 (10%)	10 (21%)	2 (4%)
Acinus, atrophy, multifocal	15 (30%)	8 (17%)	6 (12%)
Stomach	(49)		(50)
Forestomach, hyperkeratosis, multifocal			1 (2%)
Forestomach, hyperplasia, squamous, multifocal			1 (2%)
Glandular, ulcer, acute, multifocal	1 (2%)		
Tooth			(1)
Peridontal tissue, inflammation, chronic active, multifocal			1 (100%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)		(50)
Atrium left, thrombus, subacute, multifocal			1 (2%)
Myocardium, degeneration, chronic, multifocal	40 (80%)		38 (76%)
Myocardium, inflammation, acute, multifocal	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(49)
Bilateral, cortex, atrophy, diffuse		1 (2%)	
Bilateral, cortex, congestion, multifocal	1 (2%)	1 (2%)	
Bilateral, cortex, congestion, subacute, multifocal	1 (2%)		
Bilateral, cortex, degeneration, fatty, diffuse		1 (2%)	
Bilateral, cortex, degeneration, fatty, multifocal		3 (6%)	1 (2%)
Bilateral, cortex, hyperplasia, focal	1 (2%)		
Bilateral, cortex, hyperplasia, multifocal	1 (2%)	7 (14%)	2 (4%)
Bilateral, medulla, hyperplasia, multifocal	1 (2%)		2 (4%)
Bilateral, medulla, infiltration cellular, lymphocytic, acute, multifocal			1 (2%)
Capsule, hyperplasia, focal		1 (2%)	
Cortex, cyst	1 (2%)		
Cortex, cytoplasmic alteration, focal	3 (6%)	3 (6%)	1 (2%)
Cortex, cytoplasmic alteration, multifocal		1 (2%)	
Cortex, degeneration, cystic, focal	1 (2%)	1 (2%)	
Cortex, degeneration, fatty, focal	12 (24%)	7 (14%)	6 (12%)
Cortex, degeneration, fatty, multifocal	2 (4%)	1 (2%)	3 (6%)
Cortex, hyperplasia, focal	8 (16%)	6 (12%)	11 (22%)
Cortex, hyperplasia, multifocal	2 (4%)	3 (6%)	2 (4%)
Cortex, hypertrophy, focal	2 (4%)		1 (2%)
Cortex, karyomegaly, focal	3 (6%)	2 (4%)	
Cortex, necrosis, multifocal	1 (2%)		
Medulla, cyst		1 (2%)	
Medulla, hyperplasia, focal	2 (4%)		2 (4%)
Medulla, hyperplasia, multifocal	1 (2%)		5 (10%)
Medulla, karyomegaly, focal		1 (2%)	
Right, cortex, atrophy, multifocal		1 (2%)	
Parathyroid gland	(36)		(39)
Hyperplasia, glandular, multifocal			1 (3%)
Hyperplasia, multifocal	1 (3%)		
Pituitary gland	(50)	(32)	(48)
Cyst, multiple		1 (3%)	
Pars distalis, cyst	1 (2%)	3 (9%)	2 (4%)
Pars distalis, cyst, multiple	12 (24%)	7 (22%)	6 (13%)
Pars distalis, cyst, single	1 (2%)		1 (2%)
Pars distalis, hemorrhage, focal	1 (2%)	1 (3%)	
Pars distalis, hemorrhage, multifocal	4 (8%)		4 (8%)
Pars distalis, hemorrhage, subacute, multifocal			2 (4%)
Pars distalis, hyperplasia, diffuse			1 (2%)
Pars distalis, hyperplasia, focal	5 (10%)	1 (3%)	2 (4%)
Pars distalis, hyperplasia, multifocal	2 (4%)		4 (8%)
Pars distalis, necrosis, chronic, multifocal		1 (3%)	
Thyroid gland	(50)		(49)
C-cell, hyperplasia, focal			1 (2%)
C-cell, hyperplasia, multifocal	30 (60%)		25 (51%)
Follicle, cyst, single	2 (4%)		
GENERAL BODY SYSTEM			
None			

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Clitoral gland	(38)	(2)	(40)
Cyst			1 (3%)
Cyst, multiple	2 (5%)		
Hyperplasia, glandular, focal			3 (8%)
Inflammation, chronic active, focal	1 (3%)		1 (3%)
Inflammation, chronic active, multifocal	1 (3%)		
Inflammation, subacute, multifocal	1 (3%)		
Inflammation, suppurative, multifocal			1 (3%)
Necrosis, acute, focal	1 (3%)		
Necrosis, chronic active, focal	1 (3%)		
Ovary	(50)	(5)	(49)
Necrosis, coagulative, multifocal		1 (20%)	
Bilateral, periovarian tissue, cyst	1 (2%)		
Bilateral, follicle, cyst	1 (2%)		
Follicle, cyst			2 (4%)
Follicle, cyst, multiple	1 (2%)		5 (10%)
Follicle, cyst, single	2 (4%)		
Germinal epithelium, mineralization, multifocal	1 (2%)		
Left, periovarian tissue, cyst		2 (40%)	1 (2%)
Left, follicle, cyst	1 (2%)		
Periovarian tissue, cyst	1 (2%)	1 (20%)	3 (6%)
Right, periovarian tissue, cyst	1 (2%)	1 (20%)	
Uterus	(50)	(10)	(50)
Abscess	2 (4%)		
Inflammation, chronic active, multifocal	1 (2%)		
Bilateral, lumen, ectasia		1 (10%)	
Bilateral, lumen, ectasia, multifocal			1 (2%)
Cervix, diverticulum	2 (4%)	1 (10%)	1 (2%)
Cervix, fibrosis, chronic, multifocal			1 (2%)
Cervix, inflammation, chronic active, multifocal		1 (10%)	1 (2%)
Cervix, inflammation, suppurative, multifocal	1 (2%)		
Cervix, prolapse, multifocal		1 (10%)	
Endometrium, hemorrhage, multifocal		1 (10%)	
Endometrium, hyperplasia, cystic, glandular, multifocal	24 (48%)		32 (64%)
Left, lumen, ectasia, focal			1 (2%)
Lumen, ectasia, focal			1 (2%)
Lumen, ectasia, multifocal	3 (6%)		5 (10%)
Lumen, hemorrhage, subacute, focal		2 (20%)	
Right, lumen, ectasia, focal	1 (2%)	1 (10%)	
Right, lumen, ectasia, multifocal	1 (2%)	1 (10%)	1 (2%)
Serosa, inflammation, chronic, focal	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	(12)		(8)
Neutrophilia			1 (13%)
Bone marrow	(50)		(49)
Hyperplasia, neutrophil, multifocal	1 (2%)		3 (6%)
Hyperplasia, reticulum cell, multifocal	5 (10%)		
Inflammation, granulomatous, multifocal			1 (2%)
Myelofibrosis, multifocal			2 (4%)
Erythroid cell, hypoplasia, multifocal			1 (2%)
Lymph node	(48)	(47)	(50)
Hemorrhage	1 (2%)		
Inflammation, granulomatous, multifocal		1 (2%)	
Cortex, mandibular, cyst, multiple		1 (2%)	
Mandibular, angiectasis, multifocal			1 (2%)
Mandibular, depletion lymphoid, multifocal			1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Lymph node (Continued)	(48)	(47)	(50)
Mandibular, hemorrhage, multifocal	9 (19%)	5 (11%)	16 (32%)
Mandibular, hyperplasia, histiocyte, multifocal			1 (2%)
Mandibular, hyperplasia, lymphoid, multifocal	5 (10%)		3 (6%)
Mandibular, hyperplasia, plasma cell, multifocal	4 (8%)	8 (17%)	2 (4%)
Mandibular, inflammation, chronic, multifocal		1 (2%)	4 (8%)
Mandibular, inflammation, granulomatous, multifocal	4 (8%)	7 (15%)	4 (8%)
Mandibular, pigmentation, hemosiderin, multifocal		1 (2%)	1 (2%)
Mediastinal, depletion lymphoid, multifocal	1 (2%)		
Mediastinal, hemorrhage, multifocal	6 (13%)		2 (4%)
Mediastinal, inflammation, chronic, multifocal			1 (2%)
Mediastinal, inflammation, granulomatous, multifocal	6 (13%)		4 (8%)
Spleen	(50)	(48)	(50)
Lymphoid follicle, depletion lymphoid, multifocal	2 (4%)	2 (4%)	1 (2%)
Lymphoid follicle, inflammation, granulomatous, multifocal	2 (4%)		
Red pulp, congestion, focal	1 (2%)	1 (2%)	
Red pulp, fibrosis, focal		1 (2%)	
Red pulp, hematopoietic cell proliferation, multifocal	25 (50%)	17 (35%)	30 (60%)
Red pulp, hematopoietic cell proliferation, multiple		1 (2%)	
Red pulp, inflammation, chronic active, multifocal		1 (2%)	
Red pulp, inflammation, granulomatous, multifocal		1 (2%)	2 (4%)
Red pulp, necrosis, acute, focal	1 (2%)		
Red pulp, necrosis, acute, multifocal			1 (2%)
Red pulp, pigmentation, hemosiderin, multifocal	2 (4%)	3 (6%)	2 (4%)
Thymus	(39)		(47)
Depletion lymphoid, multifocal	30 (77%)		36 (77%)
Pigmentation, hemosiderin, multifocal			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(46)	(9)	(46)
Acinus, hyperplasia, cystic, multifocal	26 (57%)		27 (59%)
Acinus, hyperplasia, cystic, multiple	1 (2%)		
Skin	(50)	(2)	(50)
Abdominal, ulcer, acute, focal			1 (2%)
Axillary, subcutaneous tissue, inflammation, chronic active, multifocal	1 (2%)		
Hindlimb, subcutaneous tissue, inflammation, granulomatous, chronic active		1 (50%)	
Hindlimb, epidermis, acanthosis, multifocal		1 (50%)	
Hindlimb, epidermis, hyperkeratosis, multifocal		1 (50%)	
MUSCULOSKELETAL SYSTEM			
Bone	(49)		(50)
Femur, osteopetrosis, multifocal	7 (14%)		11 (22%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)		(48)
Cerebellum, hemorrhage, acute, focal	1 (2%)		
Cerebellum, hemorrhage, multifocal			1 (2%)
Cerebrum, compression, focal	9 (18%)		7 (15%)
Cerebrum, hemorrhage, focal			1 (2%)
Cerebrum, perivascular cuffing, focal			1 (2%)
Medulla, hemorrhage, focal			1 (2%)
Medulla, hemorrhage, multifocal	1 (2%)		
Ventricle, hydrocephalus, multifocal	3 (6%)		5 (10%)
RESPIRATORY SYSTEM			
Lung	(50)	(1)	(50)
Congestion, acute, diffuse		1 (100%)	
Congestion, acute, multifocal	2 (4%)		
Hemorrhage, acute, multifocal	2 (4%)		
Pigmentation, hemosiderin, multifocal			1 (2%)
Alveolar epithelium, hyperplasia, focal			2 (4%)
Alveolar epithelium, hyperplasia, multifocal	1 (2%)		
Bronchiole, epithelium, hyperplasia, multifocal			1 (2%)
Interstitium, inflammation, acute, focal	1 (2%)		
Interstitium, inflammation, acute, multifocal			1 (2%)
Interstitium, inflammation, chronic, focal			1 (2%)
Interstitium, inflammation, subacute, multifocal			1 (2%)
Nose	(45)		(45)
Nasolacrimal duct, inflammation, subacute, focal	5 (11%)		7 (16%)
Nasolacrimal duct, inflammation, subacute, multifocal	18 (40%)		9 (20%)
Respiratory epithelium, degeneration, multifocal	19 (42%)		17 (38%)
Submucosa, respiratory epithelium, congestion, acute, multifocal	1 (2%)		
Submucosa, respiratory epithelium, inflammation, subacute, multifocal	21 (47%)		24 (53%)
Trachea	(49)		(48)
Wall, hemorrhage, multifocal			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(1)	(4)
Hemorrhage, acute, multifocal	1 (25%)		
Lens, cataract		1 (100%)	3 (75%)
Lens, cataract, multifocal	1 (25%)		
Retina, atrophy, multifocal	1 (25%)	1 (100%)	3 (75%)
Harderian gland	(40)		(42)
Inflammation, subacute, focal			2 (5%)
Inflammation, subacute, multifocal	15 (38%)		8 (19%)
Bilateral, inflammation, subacute, multifocal	1 (3%)		2 (5%)
URINARY SYSTEM			
Kidney	(50)	(1)	(49)
Bilateral, nephropathy, chronic, multifocal	46 (92%)		33 (67%)
Bilateral, nephropathy, multifocal			1 (2%)
Cortex, casts, single	1 (2%)		
Cortex, infarct, focal			1 (2%)
Cortex, inflammation, chronic, focal	1 (2%)		1 (2%)
Left, cortex, cyst, single		1 (100%)	1 (2%)
Left, medulla, cyst, multiple	1 (2%)		
Renal tubule, degeneration, acute, multifocal	2 (4%)		1 (2%)
Renal tubule, hyperplasia, focal			1 (2%)
Renal tubule, vacuolization cytoplasmic, multifocal	1 (2%)		

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
Urinary bladder	(50)	(1)	(48)
Calculus micro observation only			1 (2%)
Lumen, calculus gross observation		1 (100%)	
Mucosa, hyperplasia, chronic, multifocal		1 (100%)	
Mucosa, hyperplasia, multifocal			1 (2%)
Mucosa, hyperplasia, squamous, multifocal			1 (2%)
Mucosa, metaplasia, squamous, multifocal			1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

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TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(42)	*(50)	(40)
Lymphoma malignant mixed	1 (2%)		
Intestine large	(48)	*(50)	(45)
Cecum, lymphoma malignant lymphocytic			1 (2%)
Intestine small	(44)	*(50)	(41)
Jejunum, Peyer's patch, lymphoma malignant mixed		1 (2%)	
Peyer's patch, lymphoma malignant mixed			1 (2%)
Liver	(50)	(49)	(48)
Hemangiosarcoma	1 (2%)	1 (2%)	
Hemangiosarcoma, multiple		1 (2%)	
Hepatocellular carcinoma	5 (10%)	7 (14%)	3 (6%)
Hepatocellular carcinoma, trabecular, multiple	1 (2%)		
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	3 (6%)	5 (10%)	6 (13%)
Hepatocellular adenoma, multiple	1 (2%)		
Lymphoma malignant histiocytic		2 (4%)	
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic			2 (4%)
Pancreas	(49)	*(50)	(45)
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Salivary glands	(50)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Stomach	(48)	*(50)	(46)
Lymphoma malignant lymphocytic			1 (2%)
Forestomach, papilloma squamous			2 (4%)
Forestomach, squamous cell carcinoma			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Lymphoma malignant lymphocytic			2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland	(49)	*(50)	(45)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Medulla, pheochromocytoma benign			1 (2%)
Spindle cell, adenoma	1 (2%)		1 (2%)
Thyroid gland	(50)	*(50)	(48)
Follicular cell, adenoma	2 (4%)		
GENERAL BODY SYSTEM			
Tissue, NOS		*(50)	(1)
Lymphoma malignant mixed			1 (100%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM			
Epididymis	(48)	*(50)	(48)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Penis	*(50)	*(50)	*(50)
Sarcoma	1 (2%)		
Preputial gland	(8)	*(50)	(8)
Sarcoma	1 (13%)		
Prostate	(48)	(49)	(49)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Testes	(48)	*(50)	(48)
Lymphoma malignant lymphocytic			1 (2%)
Interstitial cell, adenoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
Lymph node	(48)	*(50)	(47)
Sarcoma, metastatic, skin	1 (2%)		
Axillary, lymphoma malignant histiocytic		1 (2%)	
Axillary, lymphoma malignant mixed	1 (2%)		
Bronchial, lymphoma malignant mixed	1 (2%)		
Lumbar, lymphoma malignant histiocytic		1 (2%)	
Lumbar, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant lymphocytic			1 (2%)
Mandibular, lymphoma malignant mixed	1 (2%)		1 (2%)
Mesenteric, lymphoma malignant histiocytic		1 (2%)	
Mesenteric, lymphoma malignant mixed	1 (2%)		1 (2%)
Pancreatic, lymphoma malignant histiocytic		1 (2%)	
Pancreatic, lymphoma malignant lymphocytic			1 (2%)
Pancreatic, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant mixed	1 (2%)		
Spleen	(49)	(46)	(47)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant histiocytic	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic			3 (6%)
Lymphoma malignant mixed	2 (4%)		1 (2%)
Thymus	(38)	*(50)	(38)
Lymphoma malignant lymphocytic			2 (5%)
Lymphoma malignant mixed	2 (5%)		1 (3%)
INTEGUMENTARY SYSTEM			
Skin	(50)	*(50)	(49)
Papilloma squamous			1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	5 (10%)	2 (4%)
Subcutaneous tissue, fibroma, multiple			1 (2%)
Subcutaneous tissue, fibrosarcoma		5 (10%)	1 (2%)
Subcutaneous tissue, fibrosarcoma, multiple	1 (2%)		
Subcutaneous tissue, leiomyosarcoma	1 (2%)		
Subcutaneous tissue, lymphoma malignant lymphocytic			1 (2%)
Subcutaneous tissue, sarcoma	5 (10%)	3 (6%)	1 (2%)
Subcutaneous tissue, sarcoma, multiple	2 (4%)	1 (2%)	
Tail, subcutaneous tissue, sarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, skin		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant histiocytic		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		3 (6%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Fibrosarcoma, metastatic, skin		1 (2%)	
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant mixed	2 (4%)		1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenocarcinoma	1 (2%)		
Adenoma	2 (4%)	2 (4%)	4 (8%)
URINARY SYSTEM			
Kidney	(49)	*(50)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		3 (6%)
Lymphoma malignant mixed	1 (2%)		
Urinary bladder	(48)	*(50)	(46)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Hemangiosarcoma	1 (2%)	2 (4%)	
Lymphoma malignant histiocytic	1 (2%)	2 (4%)	
Lymphoma malignant mixed	2 (4%)	1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		3 (6%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	33	32	31
Dead	12	14	12
Moribund	5	4	3
Drowned			4
TUMOR SUMMARY			
Total animals with primary neoplasms **	29	29	24
Total primary neoplasms	38	37	33
Total animals with benign neoplasms	11	13	16
Total benign neoplasms	13	14	21
Total animals with malignant neoplasms	21	21	10
Total malignant neoplasms	25	23	12
Total animals with secondary neoplasms ***	1	2	
Total secondary neoplasms	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 2,4-DICHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	004	016	081	083	083	085	087	093	095	097	098	098	099	099	100	103	103	104	104	104	104	104	104	104	104
CARCASS ID	102	061	144	444	093	041	104	024	012	051	033	034	023	072	075	063	054	111	113	115	121	122	225	131	032
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	M	+	M	A	+	+	+	A	+	M	A	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Intestine large	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	M	+	M	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma											X				X			X							
Hepatocellular carcinoma, trabecular, multiple							X																		
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Lymphoma malignant mixed				X																					
Mesentery										+	+											+	+		
Pancreas	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Stomach	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Tooth								+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Spindle cell, adenoma																						X			
Islets, pancreatic	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland														+		+									
Epididymis	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Penis																+									
Sarcoma																X									
Preputial gland																+		+							+
Sarcoma																X									
Prostate	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					
Seminal vesicle		A												+		+	+						+		+
Testes	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ 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	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL
CARCASS ID	035	042	043	045	052	053	055	062	064	065	071	073	074	081	082	083	084	085	091	092	094	095	101	103	105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymphoma malignant mixed																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma								X						X												5
Hepatocellular carcinoma, trabecular, multiple																										1
Hepatocellular carcinoma, multiple									X																	1
Hepatocellular adenoma								X									X							X		3
Hepatocellular adenoma, multiple												X														1
Lymphoma malignant mixed																										1
Mesentery			+	+		+		+			+	+	+	+	+		+	+	+		+	+	+	+	+	21
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Spindle cell, adenoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	38
Pituitary gland	+	+	+	+	+	M	M	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X															X					2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																		+					+			4
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Penis						+																+	M	+	+	5
Sarcoma																										1
Preputial gland					+	+			+											+	+	+	M	+		10
Sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Seminal vesicle	+		+					+				+		+			+	+	+	+			+	+	+	17
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

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

WEEKS ON STUDY	04	06	08	08	08	08	08	09	09	09	09	09	09	09	10	10	10	10	10	10	10	10	10	10	10
	16	16	81	83	83	85	87	93	95	97	98	98	99	99	00	03	03	04	04	04	04	04	04	04	04
CARCASS ID	10	06	01	04	09	04	10	02	12	51	33	34	23	72	75	63	54	11	13	15	21	22	25	31	32
	02	61	14	44	93	41	04	24																	
HEMATOPOIETIC SYSTEM																									
Blood			+			+						+									+		+		+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin											X														
Axillary, lymphoma malignant mixed				X																					
Bronchial, lymphoma malignant mixed				X																					
Lumbar, lymphoma malignant mixed				X																					
Mandibular, lymphoma malignant mixed				X																					
Mesenteric, lymphoma malignant mixed				X																					
Pancreatic, lymphoma malignant mixed				X																					
Renal, lymphoma malignant mixed				X																					
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Lymphoma malignant histiocytic						X																			
Lymphoma malignant mixed				X																					
Thymus	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma, multiple													X												
Subcutaneous tissue, leiomyosarcoma			X																						
Subcutaneous tissue, sarcoma								X		X				X		X									
Subcutaneous tissue, sarcoma, multiple									X		X														
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant mixed				X																					
Nose	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland							+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed				X																					
Urinary bladder	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X																					

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

WEEKS ON STUDY	104	104	104	104	104	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL TISSUES TUMORS
CARCASS ID	03 5	04 2	04 3	04 5	05 2	05 3	05 5	06 2	06 4	06 5	07 1	07 3	07 4	08 1	08 2	08 3	08 4	08 5	09 1	09 2	09 4	09 5	10 1	10 3	10 5	
HEMATOPOIETIC SYSTEM																										
Blood					+								+			+			+		+	+	M			12
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, metastatic, skin																										1
Axillary, lymphoma malignant mixed																										1
Bronchial, lymphoma malignant mixed																										1
Lumbar, lymphoma malignant mixed																										1
Mandibular, lymphoma malig mixed																										1
Mesenteric, lymphoma malignant mixed																										1
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed															X											2
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	38
Lymphoma malignant mixed															X											2
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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																					X			X		2
Subcutaneous tissue, fibrosarcoma, multiple																										1
Subcutaneous tissue, leiomyosarcoma																										1
Subcutaneous tissue, sarcoma						X																				5
Subcutaneous tissue, sarcoma, multiple																										2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									2
Alveolar/bronchiolar carcinoma							X																			1
Lymphoma malignant mixed															X											2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																			+				M			1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma																X										1
Adenoma															X				X							2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic															X											1
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	015	020	057	067	068	069	073	079	088	093	094	095	096	097	098	099	103	104	105	105	105	105	105	105	105
CARCASS ID	244	261	225	242	251	221	304	284	292	283	243	272	294	212	285	305	254	252	211	213	214	215	222	223	224
ALIMENTARY SYSTEM																									
Intestine large											+														
Intestine small											A														
Jejunum, Peyer's patch, lymphoma malignant mixed																									
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hemangiosarcoma, multiple					X																				
Hepatocellular carcinoma												X	X	X		X									
Hepatocellular adenoma																					X				
Lymphoma malignant histiocytic				X																					
Mesentery																									
Stomach											+														
CARDIOVASCULAR SYSTEM																									
Heart															+										
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
ENDOCRINE SYSTEM																									
None																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Penis		+	M			+																	+		
Preputial gland	+									+														+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle			+			+																			
Testes																					+				
Interstitial cell, adenoma																					X				
HEMATOPOIETIC SYSTEM																									
Blood									M																
Lymph node			+	+						+									+		+	+			
Axillary, lymphoma malignant histiocytic																									
Lumbar, lymphoma malignant histiocytic				X																					
Mesenteric, lymphoma malignant histiocytic																									
Pancreatic, lymphoma malignant histiocytic																									
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
INTEGUMENTARY SYSTEM																									
Skin						+	+	+	+	+				+		+	+	+		+			+	+	+
Subcutaneous tissue, fibroma																									X
Subcutaneous tissue, fibrosarcoma							X			X								X							
Subcutaneous tissue, sarcoma								X									X						X		
Subcutaneous tissue, sarcoma, multiple																X									
Tail, subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	M		M	M	M	M	M	M		+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Skeletal muscle																		+							
Fibrosarcoma, metastatic, skin																		X							
NERVOUS SYSTEM																									
Brain				+																					
Lymphoma malignant histiocytic				X																					
RESPIRATORY SYSTEM																									
Lung						+									+			+							
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma															X										
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Fibrosarcoma, metastatic, skin																		X							
SPECIAL SENSES SYSTEM																									
Harderian gland																				+		+			
Adenoma																				X					
URINARY SYSTEM																									
Kidney		+							+						+			+		+					
Fibrosarcoma, metastatic, skin																		X							
Urethra									+						+										
Urinary bladder			A						+		A				+					+					

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE 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	105	TOTAL
CARCASS ID	231	232	233	234	235	241	245	253	255	262	263	264	265	271	273	274	275	281	282	291	293	295	301	302	303		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Intestine large																											1
Intestine small									+																		1
Jejunum, Peyer's patch, lymphoma malignant mixed									X																		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Hemangiosarcoma																											1
Hemangiosarcoma, multiple																											1
Hepatocellular carcinoma																		X				X			X		7
Hepatocellular adenoma				X				X							X		X										5
Lymphoma malignant histiocytic										X																	2
Mesentery																											1
Stomach					+		+							+				+					+				6
CARDIOVASCULAR SYSTEM																											
Heart																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
ENDOCRINE SYSTEM																											
None																											
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Penis											+																4
Preputial gland					+																+						5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Seminal vesicle																											2
Testes																											1
Interstitial cell, adenoma																											1
HEMATOPOIETIC SYSTEM																											
Blood																											
Lymph node			+							+				+		+							+			11
Axillary, lymphoma malignant histiocytic										X																	1
Lumbar, lymphoma malig histiocytic																											1
Mesenteric, lymphoma malignant histiocytic										X																	1
Pancreatic, lymphoma malignant histiocytic										X																	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+		46
Lymphoma malignant histiocytic										X																	1
INTEGUMENTARY SYSTEM																											
Skin	+				+					+			+		+							+		+		20
Subcutaneous tissue, fibroma										X			X									X		X		5
Subcutaneous tissue, fibrosarcoma	X									X																	5
Subcutaneous tissue, sarcoma																											3
Subcutaneous tissue, sarcoma, multiple																											1
Tail, subcutaneous tissue, sarcoma					X																						1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Skeletal muscle																											1
Fibrosarcoma, metastatic, skin																											1
NERVOUS SYSTEM																											
Brain																											1
Lymphoma malignant histiocytic																											1
RESPIRATORY SYSTEM																											
Lung	+																										4
Alveolar/bronchiolar adenoma, multiple	X																										1
Alveolar/bronchiolar carcinoma																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Fibrosarcoma, metastatic, skin																											1
SPECIAL SENSES SYSTEM																											
Harderian gland																									+		3
Adenoma																									X		2
URINARY SYSTEM																											
Kidney																						+					6
Fibrosarcoma, metastatic, skin																											1
Urethra																											2
Urinary bladder																											3

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	025	038	040	045	054	056	057	059	060	060	060	060	069	077	085	086	095	096	097	104	104	104	104	104	104
CARCASS ID	46064	46065	50053	48044	50052	49095	48085	50055	45051	45052	45054	45055	47071	47072	47074	49092	43035	50044	42044	41111	41112	41113	41114	41115	42121
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	+	A	+	+	+	A	+	+	A	A	+	M	A	+	A	+	+	+	+	+	+
Intestine large	+	A	A	+	+	+	+	+	+	+	+	+	A	+	+	M	A	+	+	+	+	+	+	+	+
Cecum, lymphoma malignant lymphocytic																									
Intestine small	A	A	A	A	+	+	+	+	+	A	+	+	A	A	+	M	A	+	+	+	+	+	+	+	+
Peyer's patch, lymphoma malignant mixed							X																		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																			X						
Hepatocellular adenoma																					X		X		
Lymphoma malignant lymphocytic																									
Mesentery					+	+		+							+			+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Pancreas	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	A	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Lymphoma malignant mixed							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach	+	A	A	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Forestomach, papilloma squamous																									
Forestomach, squamous cell carcinoma																					X				
Tooth																	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	A	+	+	+	+	M	+	+	+	+	+	A	+	+	M	A	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Medulla, pheochromocytoma benign																									
Spindle cell, adenoma																									
Islets, pancreatic	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	M	A	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	M	+	M	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	I	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS							+																		
Lymphoma malignant mixed							X																		
GENITAL SYSTEM																									
Coagulating gland																		+	+	+	+	+	+		+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Penis				+																					
Preputial gland	+	+					+		+			+		+						+					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Seminal vesicle	+					+		+						+			+	+	+						+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

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

WEEKS ON STUDY	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	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	TOTAL TISSUES TUMORS
CARCASS ID	4 2 2	4 2 3	4 2 5	4 3 1	4 3 2	4 3 3	4 3 4	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 5 3	4 6 1	4 6 2	4 6 3	4 7 3	4 7 5	4 8 1	4 8 2	4 8 3	4 9 1	4 9 3	4 9 4	5 0 1	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cecum, lymphoma malig lymphocytic				X																						1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Peyer's patch, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma										X													X			3
Hepatocellular adenoma												X		X						X					X	6
Lymphoma malignant lymphocytic				X																						1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymphoma malignant lymphocytic				X																						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic				X																						2
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic				X																						1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic				X																						1
Forestomach, papilloma squamous											X		X													2
Forestomach, squamous cell carcinoma																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic				X																						2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																										1
Medulla, pheochromocytoma benign																					X					1
Spindle cell, adenoma													X													1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	M	M	M	M	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Lymphoma malignant mixed																										1
GENITAL SYSTEM																										
Coagulating gland		+		+							+	+	+		+		+	+		+	+		+	+	+	20
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic				X																						1
Penis																								+		2
Preputial gland											+													+		9
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic				X																						1
Seminal vesicle		+		+			+			+					+	+		+								15
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic				X																						1

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

WEEKS ON STUDY	025	038	040	045	054	056	057	059	060	060	060	060	069	077	085	086	095	096	097	104	104	104	104	104	104
CARCASS ID	464	465	503	484	502	495	485	505	451	452	454	455	471	472	474	492	435	504	424	411	412	413	414	415	421
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+
Mandibular, lymphoma malignant lymphocytic																									
Mandibular, lymphoma malignant mixed							X																		
Mesenteric, lymphoma malignant mixed							X																		
Pancreatic, lymphoma malignant lymphocytic															X										
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Lymphoma malignant mixed							X																		
Thymus	+	M	M	M	+	M	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
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	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma																								X	
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lymphoma malignant lymphocytic																									
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																				X	X				
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed							X																		
Nose	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																	+			+	+	+	+	+	+
Adenoma																					X				X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Urinary bladder	+	M	A	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
CARCASS ID	42 2	42 3	42 5	43 1	43 2	43 3	43 4	44 1	44 2	44 3	44 4	44 5	45 3	46 1	46 2	46 3	47 3	47 5	48 1	48 2	48 3	49 1	49 3	49 4	50 1	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood				+						+				+	+									+	+	6
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Mandibular, lymphoma malignant lymphocytic				X																						1
Mandibular, lymphoma malig mixed																										1
Mesenteric, lymphoma malignant mixed																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic				X											X											3
Lymphoma malignant mixed																										1
Thymus	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	38
Lymphoma malignant lymphocytic				X																						2
Lymphoma malignant mixed																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																				X						1
Subcutaneous tissue, fibroma								X																		2
Subcutaneous tissue, fibroma, multiple	X																									1
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, lymphoma malignant lymphocytic				X																						1
Subcutaneous tissue, sarcoma																		X								1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X			X					X															3
Alveolar/bronchiolar carcinoma																										2
Lymphoma malignant lymphocytic				X											X											2
Lymphoma malignant mixed																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye										+																1
Harderian gland		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	30
Adenoma										X										X						4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic				X											X											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic				X																						1

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Control	5,000 ppm	10,000 ppm
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	6.1%	6.3%	12.9%
Terminal Rates (c)	2/33 (6%)	2/32 (6%)	4/31 (13%)
Day of First Observation	727	727	727
Life Table Tests (d)	P=0.227	P=0.685	P=0.307
Logistic Regression Tests (d)	P=0.227	P=0.685	P=0.307
Cochran-Armitage Trend Test (d)	P=0 252		
Fisher Exact Test (d)		P=0.691	P=0.339
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	9 1%	6.3%	12.9%
Terminal Rates (c)	3/33 (9%)	2/32 (6%)	4/31 (13%)
Day of First Observation	727	727	727
Life Table Tests (d)	P=0 385	P=0.514N	P=0.465
Logistic Regression Tests (d)	P=0.385	P=0.514N	P=0.465
Cochran-Armitage Trend Test (d)	P=0 417		
Fisher Exact Test (d)		P=0.500N	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	5/49 (10%)	6/48 (13%)
Adjusted Rates (b)	12.1%	15.6%	19.4%
Terminal Rates (c)	4/33 (12%)	5/32 (16%)	6/31 (19%)
Day of First Observation	727	727	727
Life Table Tests (d)	P=0.267	P=0.480	P=0.327
Logistic Regression Tests (d)	P=0.267	P=0.480	P=0.327
Cochran-Armitage Trend Test (d)	P=0.285		
Fisher Exact Test (d)		P=0.487	P=0.344
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	7/50 (14%)	7/49 (14%)	3/48 (6%)
Adjusted Rates (b)	18.6%	18.7%	9.4%
Terminal Rates (c)	4/33 (12%)	3/32 (9%)	2/31 (6%)
Day of First Observation	605	665	675
Life Table Tests (d)	P=0.203N	P=0 567	P=0.222N
Logistic Regression Tests (d)	P=0.209N	P=0.587	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.151N		
Fisher Exact Test (d)		P=0.597	P=0.176N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	12/49 (24%)	9/48 (19%)
Adjusted Rates (b)	27 0%	32 7%	28.1%
Terminal Rates (c)	7/33 (21%)	8/32 (25%)	8/31 (26%)
Day of First Observation	605	665	675
Life Table Tests (d)	P=0.541	P=0.364	P=0.592N
Logistic Regression Tests (d)	P=0.430	P=0.352	P=0.494
Cochran-Armitage Trend Test (d)	P=0.492N		
Fisher Exact Test (d)		P=0 384	P=0 540N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	(e) 1/4 (25%)	3/50 (6%)
Adjusted Rates (b)	6.1%		9.7%
Terminal Rates (c)	2/33 (6%)		3/31 (10%)
Day of First Observation	727		727
Life Table Test (d)			P=0.471
Logistic Regression Test (d)			P=0 471
Fisher Exact Test (d)			P=0.500

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	5,000 ppm	10,000 ppm
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	(e) 2/4 (50%)	5/50 (10%)
Adjusted Rates (b)	9.1%		16.1%
Terminal Rates (c)	3/33 (9%)		5/31 (16%)
Day of First Observation	727		727
Life Table Test (d)			P=0.320
Logistic Regression Test (d)			P=0.320
Fisher Exact Test (d)			P=0.357
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	6.1%	15.6%	9.7%
Terminal Rates (c)	2/33 (6%)	5/32 (16%)	3/31 (10%)
Day of First Observation	727	727	727
Life Table Tests (d)	P=0.387	P=0.201	P=0.471
Logistic Regression Tests (d)	P=0.387	P=0.201	P=0.471
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.218	P=0.500
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	2.6%	13.3%	3.2%
Terminal Rates (c)	0/33 (0%)	2/32 (6%)	1/31 (3%)
Day of First Observation	687	510	727
Life Table Tests (d)	P=0.535	P=0.099	P=0.731
Logistic Regression Tests (d)	P=0.562	P=0.103	P=0.724
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.102	P=0.753N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	8.5%	24.9%	12.9%
Terminal Rates (c)	2/33 (6%)	6/32 (19%)	4/31 (13%)
Day of First Observation	687	510	727
Life Table Tests (d)	P=0.374	P=0.058	P=0.455
Logistic Regression Tests (d)	P=0.320	P=0.054	P=0.398
Cochran-Armitage Trend Test (d)	P=0.436		
Fisher Exact Test (d)		P=0.061	P=0.500
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	7/50 (14%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	16.9%	13.7%	3.2%
Terminal Rates (c)	1/33 (3%)	2/32 (6%)	1/31 (3%)
Day of First Observation	651	547	727
Life Table Tests (d)	P=0.050N	P=0.432N	P=0.063N
Logistic Regression Tests (d)	P=0.034N	P=0.388N	P=0.046N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.380N	P=0.030N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	10/50 (20%)	2/50 (4%)
Adjusted Rates (b)	19.1%	25.5%	6.5%
Terminal Rates (c)	1/33 (3%)	4/32 (13%)	2/31 (6%)
Day of First Observation	651	510	727
Life Table Tests (d)	P=0.106N	P=0.356	P=0.092N
Logistic Regression Tests (d)	P=0.072N	P=0.389	P=0.071N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.398	P=0.046N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	5,000 ppm	10,000 ppm
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	14/50 (28%)	5/50 (10%)
Adjusted Rates (b)	24.1%	36.1%	16.1%
Terminal Rates (c)	3/33 (9%)	8/32 (25%)	5/31 (16%)
Day of First Observation	651	510	727
Life Table Tests (d)	P=0.215N	P=0.220	P=0.211N
Logistic Regression Tests (d)	P=0.209N	P=0.221	P=0.219N
Cochran-Armitage Trend Test (d)	P=0.127N		
Fisher Exact Test (d)		P=0.241	P=0.131N
Forestomach: Squamous Papilloma or Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	(f) 0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	9.7%
Terminal Rates (c)	0/33 (0%)	0/32 (0%)	3/31 (10%)
Day of First Observation			727
Life Table Tests (d)	P=0.033	(g)	P=0.110
Logistic Regression Tests (d)	P=0.033	(g)	P=0.110
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(g)	P=0.121
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	7.2%	8.2%	11.1%
Terminal Rates (c)	1/33 (3%)	2/32 (6%)	2/31 (6%)
Day of First Observation	575	469	394
Life Table Tests (d)	P=0.354	P=0.637	P=0.423
Logistic Regression Tests (d)	P=0.456	P=0.653N	P=0.539
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661N	P=0.500

(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) Gross lesions and target organs in low dose group examined according to protocol (see Table 6); seven stomachs were examined microscopically.
(g) No P value is reported because no tumors were observed in the 5,000-ppm and control groups.

TABLE C4. HISTORICAL INCIDENCE OF STOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	0/47
N-Phenyl-2-naphthylamine	0/43
C.I. Disperse Yellow 3	0/50
D & C Red No. 9	0/47
C.I. Solvent Yellow 14	0/47
Rotenone	(b) 1/45
l-Ascorbic acid	0/50
TOTAL	1/329 (0.3%)
SD (c)	0.84%
Range (d)	
High	1/45
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 8/1,986 (0.4%)
SD (c)	0.94%
Range (d)	
High	2/49
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Squamous cell papilloma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes six squamous cell papillomas, one papilloma, NOS, and one squamous cell carcinoma

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large	(48)	(1)	(45)
Colon, parasite metazoan, single	1 (2%)		1 (2%)
Intestine small	(44)	(1)	(41)
Thrombus, acute, multifocal	1 (2%)		
Jejunum, Peyer's patch, hyperplasia, lymphoid, multifocal	1 (2%)		
Liver	(50)	(49)	(48)
Basophilic focus, multiple	1 (2%)		1 (2%)
Basophilic focus, single	2 (4%)	1 (2%)	2 (4%)
Inflammation, granulomatous, multifocal	1 (2%)		
Inflammation, subacute, multifocal		1 (2%)	1 (2%)
Bile duct, hyperplasia, multifocal	1 (2%)		
Caudate lobe, necrosis, chronic active, focal		1 (2%)	
Hepatocyte, cytomegaly		1 (2%)	
Hepatocyte, cytomegaly, diffuse		1 (2%)	
Hepatocyte, cytomegaly, multifocal		1 (2%)	
Hepatocyte, necrosis, acute, diffuse			3 (6%)
Hepatocyte, necrosis, acute, focal			1 (2%)
Hepatocyte, necrosis, acute, multifocal	2 (4%)	6 (12%)	
Hepatocyte, necrosis, coagulative, subacute, multifocal	1 (2%)		
Hepatocyte, nuclear alteration, diffuse	2 (4%)		
Hepatocyte, nuclear alteration, focal	15 (30%)	27 (55%)	18 (38%)
Hepatocyte, nuclear alteration, multifocal	2 (4%)	3 (6%)	
Hepatocyte, syncytial alteration, diffuse	11 (22%)	33 (67%)	42 (88%)
Hepatocyte, vacuolization cytoplasmic, focal			1 (2%)
Sinusoid, infiltration cellular, polymorphonuclear, diffuse		1 (2%)	
Mesentery	(21)	(1)	(37)
Fat, necrosis, acute, diffuse			1 (3%)
Fat, necrosis, multifocal		1 (100%)	
Pancreas	(49)		(45)
Acinus, atrophy, focal			2 (4%)
Salivary glands	(50)		(49)
Periductular, infiltration cellular, lymphocytic, multifocal			1 (2%)
Stomach	(48)	(6)	(46)
Forestomach, epithelium, hyperplasia, focal	5 (10%)	6 (86%)	4 (9%)
Glandular, dysplasia, focal	1 (2%)		
Glandular, inflammation, acute, focal			1 (2%)
Tooth	(40)		(34)
Peridontal tissue, inflammation, acute, focal	2 (5%)		1 (3%)
Peridontal tissue, inflammation, acute, multifocal	2 (5%)		1 (3%)
Peridontal tissue, inflammation, chronic active, focal	6 (15%)		
Peridontal tissue, inflammation, chronic active, multifocal	1 (3%)		2 (6%)
Peridontal tissue, inflammation, subacute, focal			1 (3%)
Pulp, inflammation, acute, focal	3 (8%)		
Pulp, inflammation, necrotizing, acute, focal			1 (3%)
Pulp, necrosis, acute, diffuse			1 (3%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(1)	(50)
Myocardium, inflammation, acute, multifocal			1 (2%)
Myocardium, inflammation, chronic, focal	1 (2%)		
Myocardium, inflammation, subacute, multifocal			1 (2%)
Myocardium, inflammation, suppurative, acute, focal			1 (2%)
Ventricle right, necrosis, chronic, focal			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(49)		(45)
Accessory adrenal cortical nodule			1 (2%)
Accessory adrenal cortical nodule, focal			1 (2%)
Cortex, degeneration, fatty, focal	1 (2%)		
Cortex, focal cellular change	4 (8%)		4 (9%)
Cortex, focal cellular change, multifocal	1 (2%)		2 (4%)
Cortex, hyperplasia, focal	3 (6%)		1 (2%)
Cortex, hypertrophy			3 (7%)
Medulla, hyperplasia, focal	1 (2%)		1 (2%)
Spindle cell, hyperplasia, focal			1 (2%)
Spindle cell, hyperplasia, multifocal	7 (14%)		5 (11%)
Parathyroid gland	(38)		(35)
Infiltration cellular, lymphocytic, focal	1 (3%)		
Pituitary gland	(45)		(47)
Pars distalis, inflammation, acute, focal			1 (2%)
Thyroid gland	(50)		(48)
Follicle, cyst, multiple			2 (4%)
Follicle, cyst, single	5 (10%)		2 (4%)
Follicular cell, hyperplasia, focal	1 (2%)		
Follicular cell, hyperplasia, multifocal	2 (4%)		1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland	(4)		(20)
Wall, inflammation, acute, multifocal	1 (25%)		
Epididymis	(48)		(48)
Granuloma sperm, focal	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
Epithelium, inflammation, necrotizing, diffuse			1 (2%)
Penis	(5)	(4)	(2)
Inflammation, acute, focal	1 (20%)		1 (50%)
Preputial gland	(10)	(5)	(9)
Abscess, chronic, focal	3 (30%)	1 (20%)	1 (11%)
Abscess, subacute, focal			1 (13%)
Bilateral, abscess, chronic	2 (20%)		
Bilateral, inflammation, granulomatous, suppurative, multifocal	1 (10%)	1 (20%)	
Duct, ectasia, focal	1 (10%)	1 (20%)	2 (22%)
Duct, ectasia, multifocal	1 (10%)	1 (20%)	3 (33%)
Left, abscess, chronic, focal		1 (20%)	
Right, abscess, chronic, focal	1 (10%)		
Right, abscess, chronic active, focal		1 (20%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENITAL SYSTEM (Continued)			
Prostate	(48)	(49)	(49)
Dilatation		1 (2%)	1 (2%)
Dilatation, diffuse		2 (4%)	1 (2%)
Granuloma, focal			1 (2%)
Inflammation, acute, diffuse	1 (2%)		1 (2%)
Inflammation, acute, multifocal			5 (10%)
Inflammation, necrotizing, subacute, multifocal		1 (2%)	
Inflammation, suppurative, acute, multifocal			1 (2%)
Artery, inflammation, chronic, multifocal		1 (2%)	
Seminal vesicle	(17)	(2)	(15)
Dilatation			3 (20%)
Dilatation, diffuse		2 (100%)	
Inflammation, acute, focal	1 (6%)		
Lumen, dilatation			2 (13%)
Lumen, dilatation, diffuse	1 (6%)		1 (7%)
Parenchyma, inflammation, acute, multifocal			1 (7%)
Serosa, inflammation, acute, diffuse			1 (7%)
Testes	(48)	(1)	(48)
Germinal epithelium, atrophy, diffuse			1 (2%)
Germinal epithelium, atrophy, focal	1 (2%)		
Germinal epithelium, atrophy, multifocal	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	(12)		(6)
Leukocytosis	1 (8%)		
Neutrophilia			1 (17%)
Bone marrow	(50)		(49)
Femoral, hyperplasia, neutrophil, diffuse	1 (2%)		1 (2%)
Femoral, hypoplasia, focal	1 (2%)		
Femoral, thrombus, subacute, focal			1 (2%)
Lymph node	(48)	(11)	(47)
Inguinal, hyperplasia, lymphoid, diffuse	1 (2%)		
Inguinal, infiltration cellular, plasma cell, diffuse	1 (2%)		
Lumbar, hemorrhage, acute, diffuse	1 (2%)		
Lumbar, hyperplasia, plasma cell, diffuse	1 (2%)		
Lumbar, infiltration cellular, plasma cell, diffuse	1 (2%)		
Lumbar, infiltration cellular, plasma cell, focal		1 (9%)	
Lumbar, infiltration cellular, polymorphonuclear, diffuse	1 (2%)		
Mandibular, depletion lymphoid, diffuse			4 (9%)
Mandibular, hematopoietic cell proliferation, diffuse	1 (2%)		
Mandibular, hyperplasia, lymphoid, diffuse	1 (2%)		1 (2%)
Mandibular, infiltration cellular, plasma cell, diffuse	3 (6%)		1 (2%)
Mediastinal, depletion lymphoid, diffuse			1 (2%)
Mesenteric, angiectasis, diffuse	10 (21%)	4 (36%)	3 (6%)
Mesenteric, angiectasis, multifocal	1 (2%)	1 (9%)	1 (2%)
Mesenteric, erythrophagocytosis, diffuse	1 (2%)		
Mesenteric, hematopoietic cell proliferation, diffuse	5 (10%)	1 (9%)	
Mesenteric, inflammation, chronic			1 (2%)
Pancreatic, angiectasis, diffuse			1 (2%)
Pancreatic, angiectasis, multifocal		2 (18%)	
Pancreatic, hematopoietic cell proliferation, diffuse		2 (18%)	
Pancreatic, inflammation, acute, diffuse	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(49)	(46)	(47)
Inflammation, acute, multifocal			1 (2%)
Capsule, fibrosis, focal	1 (2%)		
Lymphoid follicle, depletion lymphoid, multifocal	1 (2%)	4 (9%)	10 (21%)
Lymphoid follicle, hyperplasia, diffuse			1 (2%)
Lymphoid follicle, hyperplasia, lymphoid, diffuse	1 (2%)		
Lymphoid follicle, hyperplasia, lymphoid, focal	1 (2%)		
Lymphoid follicle, necrosis, acute, multifocal			1 (2%)
Red pulp, angiectasis, multifocal			1 (2%)
Red pulp, hematopoietic cell proliferation, diffuse	10 (20%)	11 (24%)	3 (6%)
Red pulp, infiltration cellular, plasma cell, focal	1 (2%)		
Thymus	(38)		(38)
Depletion lymphoid, diffuse	3 (8%)		2 (5%)
Cortex, cyst, single			1 (3%)
Medulla, cyst, multiple			1 (3%)
Thymocyte, necrosis, acute, diffuse	1 (3%)		8 (21%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(21)	(49)
Acanthosis, diffuse	1 (2%)		
Acanthosis, focal	1 (2%)		
Hyperkeratosis, diffuse	1 (2%)		
Inflammation, acute, focal	1 (2%)		
Inflammation, subacute, focal	1 (2%)		
Necrosis, acute, diffuse			1 (2%)
Abdominal, inflammation, chronic, focal			1 (2%)
Abdominal, ulcer, acute, focal			1 (2%)
Abdominal, ulcer, acute, multifocal			2 (4%)
Back, acanthosis, focal			2 (4%)
Back, alopecia, focal		1 (5%)	
Back, fibrosis, diffuse	2 (4%)		
Back, fibrosis, focal	1 (2%)		5 (10%)
Back, fibrosis, multifocal			1 (2%)
Back, hyperplasia, pseudoepitheliomatous, diffuse	1 (2%)		
Back, inflammation, chronic, diffuse	1 (2%)		
Back, inflammation, chronic active, diffuse	1 (2%)		
Back, ulcer, acute, diffuse	1 (2%)		
Back, ulcer, acute, focal	3 (6%)		2 (4%)
Back, ulcer, acute, multifocal			1 (2%)
Back, ulcer, chronic active, focal	1 (2%)		
Back, ulcer, chronic active, multifocal	2 (4%)		1 (2%)
Dermis, fibrosis, focal	1 (2%)		
Dermis, inflammation, subacute, focal	1 (2%)		
Face, ulcer, chronic active, multifocal	1 (2%)		
Face, subcutaneous tissue, granuloma, focal			1 (2%)
Face, subcutaneous tissue, inflammation, chronic active, focal	1 (2%)		
Hindlimb, subcutaneous tissue, inflammation, granulomatous, chronic, focal			1 (2%)
Neck, subcutaneous tissue, inflammation, acute, focal	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
INTEGUMENTARY SYSTEM			
Skin (Continued)	(50)	(21)	(49)
Prepuce, inflammation, acute, focal		1 (5%)	
Prepuce, inflammation, acute, multifocal			1 (2%)
Prepuce, inflammation, chronic active, focal			1 (2%)
Prepuce, inflammation, granulomatous, necrotizing, focal		2 (10%)	
Prepuce, inflammation, necrotizing, acute, focal		2 (10%)	
Prepuce, inflammation, necrotizing, acute, multifocal		1 (5%)	
Prepuce, inflammation, necrotizing, chronic, focal		1 (5%)	1 (2%)
Prepuce, ulcer, acute, focal	1 (2%)		
Right, inflammation, chronic active, focal	1 (2%)		
Subcutaneous tissue, granuloma, focal			1 (2%)
Subcutaneous tissue, granuloma, multiple			1 (2%)
Subcutaneous tissue, inflammation, acute, diffuse			1 (2%)
Subcutaneous tissue, inflammation, acute, focal	1 (2%)		1 (2%)
Subcutaneous tissue, inflammation, chronic, diffuse	1 (2%)		
Subcutaneous tissue, inflammation, chronic, focal			1 (2%)
Subcutaneous tissue, inflammation, granulomatous, focal	1 (2%)		3 (6%)
Thoracic, fibrosis, focal	1 (2%)		
Thoracic, inflammation, chronic active, diffuse		1 (5%)	
Thoracic, inflammation, chronic active, focal			1 (2%)
Thoracic, ulcer, chronic active, multifocal	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(39)	(50)
Hyperostosis		1 (3%)	1 (2%)
Bilateral, joint, tarsal, arthrosis, chronic	31 (62%)	33 (85%)	18 (36%)
Bilateral, joint, tarsal, metaplasia, osseous, diffuse		1 (3%)	
Bilateral, joint, tarsal, metaplasia, osseous, multifocal			1 (2%)
Joint, tarsal, arthrosis, chronic		1 (3%)	
Joint, phalanges, inflammation, chronic active, focal		1 (3%)	
Left, joint, tarsal, metaplasia, osseous, multifocal			1 (2%)
Right, joint, tarsal, inflammation, chronic active, diffuse	1 (2%)		
Unilateral, joint, tarsal, arthrosis, chronic	9 (18%)	1 (3%)	11 (22%)
NERVOUS SYSTEM			
Brain	(50)	(1)	(50)
Hemorrhage, acute, multifocal		1 (100%)	
Cerebellum, perivascular cuffing, focal	1 (2%)		
Cerebrum, inflammation, acute, focal			1 (2%)
Fourth ventricle, lateral ventricle, hydrocephalus			1 (2%)
Lateral ventricle, hydrocephalus			1 (2%)
Meninges, perivascular cuffing, focal	1 (2%)		
Meninges, perivascular cuffing, multifocal	1 (2%)		
Thalamus, mineralization	2 (4%)		3 (6%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(4)	(50)
Edema, subacute, multifocal			1 (2%)
Foreign body, multifocal			5 (10%)
Hemorrhage, subacute, diffuse	1 (2%)		
Infarct, acute, multifocal		1 (25%)	
Infiltration cellular, histiocytic, diffuse	1 (2%)		
Infiltration cellular, histiocytic, focal	1 (2%)		
Inflammation, acute, multifocal	1 (2%)		
Alveolar epithelium, hyperplasia, focal	6 (12%)		3 (6%)
Capillary, infiltration cellular, polymorphonuclear, acute, diffuse	1 (2%)		
Capillary, infiltration cellular, polymorphonuclear, diffuse	1 (2%)		
Interstitium, infiltration cellular, polymorphonuclear, acute, diffuse			1 (2%)
Interstitium, inflammation, acute, diffuse			1 (2%)
Interstitium, inflammation, acute, multifocal			1 (2%)
Interstitium, inflammation, subacute, multifocal	1 (2%)		
Mediastinum, infiltration cellular, lymphocytic, multifocal			1 (2%)
Peribronchial, infiltration cellular, lymphocytic, multifocal			1 (2%)
Right, edema, chronic, diffuse	1 (2%)		
Right, diaphragmatic lobe, edema, subacute, focal			1 (2%)
Nose	(43)		(34)
Mucosa, inflammation, acute	1 (2%)		
Mucosa, inflammation, acute, multifocal	2 (5%)		
Nasolacrimal duct, inflammation, acute, multifocal	1 (2%)		
Septum, inflammation, acute, focal			1 (3%)
SPECIAL SENSES SYSTEM			
Eye	(1)		(1)
Atrophy	1 (100%)		
Harderian gland	(44)	(3)	(30)
Hyperplasia, focal		1 (33%)	
Bilateral, hyperplasia, multifocal			1 (3%)
Right, hyperplasia, focal			1 (3%)
URINARY SYSTEM			
Kidney	(49)	(6)	(49)
Inflammation, acute, multifocal			2 (4%)
Inflammation, chronic, focal			1 (2%)
Inflammation, subacute, multifocal		1 (17%)	
Bilateral, infarct, acute, multifocal		1 (17%)	
Bilateral, inflammation, chronic, multifocal			1 (2%)
Bilateral, inflammation, suppurative, acute, multifocal		1 (17%)	1 (2%)
Cortex, cyst, focal	1 (2%)		
Cortex, infarct, chronic, focal	1 (2%)		
Cortex, inflammation, acute, focal	1 (2%)		
Cortex, metaplasia, osseous, focal			1 (2%)
Cortex, renal tubule, necrosis, acute, multifocal			1 (2%)
Corticomedullary junction, angiectasis, multifocal	1 (2%)		
Corticomedullary junction, metaplasia, osseous, focal			1 (2%)
Corticomedullary junction, mineralization, multifocal			4 (8%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
Kidney (Continued)	(49)	(6)	(49)
Corticomedullary junction, thrombus, chronic, focal	1 (2%)		
Corticomedullary junction, renal tubule, mineralization, multifocal		1 (17%)	
Left, inflammation, chronic active, diffuse	1 (2%)		
Pelvis, inflammation, acute, diffuse		1 (17%)	
Pelvis, inflammation, suppurative, acute, multifocal			1 (2%)
Pelvis, mineralization, focal			1 (2%)
Renal tubule, cytoplasmic alteration, multifocal			1 (2%)
Renal tubule, dilatation, diffuse		2 (33%)	2 (4%)
Renal tubule, dilatation, focal	1 (2%)		
Renal tubule, necrosis, acute, diffuse		1 (17%)	
Renal tubule, necrosis, subacute, diffuse	1 (2%)		
Renal tubule, regeneration, focal	3 (6%)		4 (8%)
Renal tubule, regeneration, multifocal	8 (16%)		4 (8%)
Right, atrophy		1 (17%)	
Right, inflammation, chronic active, diffuse		1 (17%)	
Urethra		(2)	
Concretion, focal		2 (100%)	
Transitional epithelium, necrosis, acute, focal		1 (50%)	
Urinary bladder	(48)	(3)	(46)
Calculus gross observation		1 (33%)	
Lumen, ectasia		2 (67%)	
Mucosa, necrosis, focal, single			1 (2%)
Serosa, inflammation, acute, multifocal			1 (2%)
Submucosa, inflammation, acute, diffuse	1 (2%)	1 (33%)	

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

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TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(46)	*(50)	(45)
Papilloma	1 (2%)		
Intestine small	(48)	*(50)	(47)
Jejunum, Peyer's patch, lymphoma malignant lymphocytic	4 (8%)		
Jejunum, Peyer's patch, lymphoma malignant undifferentiated cell type	1 (2%)		
Liver	(50)	*(50)	(50)
Hepatocellular carcinoma	2 (4%)		1 (2%)
Hepatocellular adenoma		2 (4%)	
Lymphoma malignant histiocytic	3 (6%)		
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)
Liposarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		
Sarcoma, metastatic, skin			1 (2%)
Pancreas	(49)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant undifferentiated cell type			1 (2%)
Salivary glands	(49)	*(50)	(47)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Stomach	(49)	*(50)	(48)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed			1 (2%)
Forestomach, squamous cell carcinoma	1 (2%)		
Forestomach, squamous papilloma	3 (6%)	3 (6%)	
Glandular, hepatocellular carcinoma, metastatic	1 (2%)		
Tooth	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(49)	*(50)	(50)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)	
Sarcoma, metastatic, skin			1 (2%)
Medulla, pheochromocytoma benign	2 (4%)		2 (4%)
Spindle cell, adenoma	1 (2%)		2 (4%)
Islets, pancreatic	(49)	*(50)	(47)
Adenoma			1 (2%)
Pituitary gland	(49)	*(50)	(48)
Lymphoma malignant lymphocytic			1 (2%)
Pars distalis, adenocarcinoma			1 (2%)
Pars distalis, adenoma	4 (8%)		3 (6%)
Pars intermedia, adenoma			1 (2%)
Thyroid gland	(49)	*(50)	(47)
Follicular cell, adenoma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(48)	*(46)	(48)
Choriocarcinoma			1 (2%)
Cystadenoma			1 (2%)
Granulosa cell tumor		1 (2%)	1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		
Mesothelioma benign	1 (2%)		
Bilateral, lymphoma malignant lymphocytic		1 (2%)	
Periovarian tissue, lymphoma malignant mixed			1 (2%)
Uterus	(49)	*(46)	(49)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic		2 (4%)	1 (2%)
Lymphoma malignant mixed			1 (2%)
Polyp stromal	2 (4%)	2 (4%)	1 (2%)
Sarcoma			1 (2%)
Sarcoma stromal			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	(13)	*(46)	(7)
Lymphoma malignant mixed			1 (14%)
Bone marrow	(50)	*(46)	(50)
Hemangiosarcoma, metastatic, spleen	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	2 (4%)		
Lymph node	(48)	*(46)	(46)
Lymphoma malignant lymphocytic		1 (2%)	
Sarcoma, metastatic, skin			1 (2%)
Lumbar, lymphoma malignant histiocytic	1 (2%)		
Lumbar, lymphoma malignant lymphocytic	1 (2%)	2 (4%)	
Lumbar, mediastinal, mandibular, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant histiocytic	2 (4%)		
Mandibular, lymphoma malignant lymphocytic	2 (4%)		1 (2%)
Mandibular, lymphoma malignant mixed	1 (2%)		
Mandibular, lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant histiocytic	1 (2%)		
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, lymphoma malignant mixed	1 (2%)		1 (2%)
Mesenteric, lymphoma malignant histiocytic	1 (2%)		
Mesenteric, lymphoma malignant lymphocytic		1 (2%)	
Mesenteric, lymphoma malignant undifferentiated cell type			1 (2%)
Pancreatic, lymphoma malignant lymphocytic	1 (2%)		
Pancreatic, lymphoma malignant mixed	1 (2%)		
Renal, lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Spleen	(49)	*(46)	(49)
Hemangiosarcoma	1 (2%)		
Liposarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	2 (4%)	1 (2%)
Lymphoma malignant mixed	2 (4%)	3 (7%)	2 (4%)
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 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(47)	*(46)	(42)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	
Lymphoma malignant mixed	1 (2%)		1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(19)	*(46)	(29)
Adenocarcinoma	1 (5%)		
Basosquamous tumor benign		1 (2%)	
Skin	(48)	*(46)	(49)
Lymphoma malignant lymphocytic			1 (2%)
Sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, liposarcoma			1 (2%)
Subcutaneous tissue, lymphoma malignant lymphocytic	1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(46)	(50)
Lymphoma malignant lymphocytic		1 (2%)	
Skeletal muscle	*(50)	*(46)	*(50)
Lymphoma malignant lymphocytic		2 (4%)	1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(46)	(48)
Lymphoma malignant lymphocytic			1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	*(46)	(50)
Adenocarcinoma, metastatic, harderian gland			1 (2%)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Liposarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Nose	(48)	*(46)	(44)
Adenocarcinoma, metastatic, harderian gland			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic			1 (2%)
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(46)	*(50)
Schwannoma malignant	1 (2%)		
Harderian gland	*(50)	*(46)	*(50)
Adenocarcinoma			1 (2%)
Adenoma	1 (2%)		2 (4%)
URINARY SYSTEM			
Kidney	(49)	*(46)	(50)
Lymphoma malignant histiocytic	2 (4%)		
Lymphoma malignant lymphocytic	3 (6%)		
Lymphoma malignant mixed	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
Urinary bladder	(48)	*(46)	(47)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(46)	*(50)
Lymphoma malignant undifferentiated cell	1 (2%)		1 (2%)
Lymphoma malignant mixed	2 (4%)	3 (7%)	2 (4%)
Lymphoma malignant lymphocytic	6 (12%)	3 (7%)	1 (2%)
Lymphoma malignant histiocytic	3 (6%)		
Hemangiosarcoma	1 (2%)		
Mesothelioma benign	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	45	40	43
Dead	4	10	5
Moribund	1		2
TUMOR SUMMARY			
Total animals with primary neoplasms **	26	14	22
Total primary neoplasms	38	16	28
Total animals with benign neoplasms	16	8	10
Total benign neoplasms	19	9	15
Total animals with malignant neoplasms	16	6	12
Total malignant neoplasms	19	6	12
Total animals with secondary neoplasms ***	3		3
Total secondary neoplasms	3		8
Total animals with neoplasms-- uncertain benign or malignant		1	1
Total uncertain neoplasms		1	1

* 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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: UNTREATED CONTROL

WEEKS ON STUDY	0 8 1	0 8 3	0 9 6	0 9 7	0 9 9	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	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
CARCASS ID	1 3 3	1 2 1	2 0 2	1 7 1	1 3 2	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 2 2	1 2 3	1 2 4	1 2 5	1 3 1	1 3 4	1 3 5	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 1	1 5 2	1 5 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Papilloma									X																
Intestine large	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Jejunum, Peyer's patch, lymphoma malignant lymphocytic																									
Jejunum, Peyer's patch, lymphoma malignant undifferentiated cell type								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X							X			
Lymphoma malignant histiocytic				X																					X
Lymphoma malignant lymphocytic																									
Mesentery	+			+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Salivary glands	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Stomach	+	+	+	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Forestomach, squamous cell carcinoma																									
Forestomach, squamous papilloma											X	X													
Glandular, hepatocellular carcinoma, metastatic															X										
Tooth			+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Medulla, pheochromocytoma benign																									
Spindle cell, adenoma																									
Islets, pancreatic	+	+	+	+	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	M	+	+	+	+	-	+	+	M	M	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X				X				X		
Thyroid gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	A	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic																		X							
Lymphoma malignant mixed											X														
Mesothelioma benign																									
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Polyp stromal																									

+ 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	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	154	155	161	162	163	164	165	172	173	174	175	181	182	183	184	185	191	192	193	194	195	201	203	204	205	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Papilloma																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Jejunum, Peyer's patch, lymphoma malignant lymphocytic				X																X		X			X	4
Jejunum, Peyer's patch, lymphoma malignant undifferentiated cell type																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Lymphoma malignant histiocytic																								X		3
Lymphoma malignant lymphocytic																									X	1
Mesentery	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																								X		2
Lymphoma malignant lymphocytic																				X						1
Lymphoma malignant mixed																	X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																	X									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Forestomach, squamous cell carcinoma				X																						1
Forestomach, squamous papilloma																	X									3
Glandular, hepatocellular carcinoma, metastatic																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																								X		1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										1
Medulla, pheochromocytoma benign																			X			X				2
Spindle cell, adenoma						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																	X									4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																					X					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																								X		2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Mesothelioma benign																							X			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																								X		2
Polyp stromal									X					X												2

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

WEEKS ON STUDY	081	083	096	097	099	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	133	121	202	171	132	111	112	113	114	115	122	123	124	125	131	134	135	141	142	143	144	145	151	152	153
HEMATOPOIETIC SYSTEM																									
Blood								+			+			+	+									+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed											X														
Lymph node	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant histiocytic				X																					
Lumbar, lymphoma malignant lymphocytic																									
Lumbar, mediastinal, mandibular, lymphoma malignant mixed											X														
Mandibular, lymphoma malignant histiocytic				X																					
Mandibular, lymphoma malignant lymphocytic																									
Mandibular, lymphoma malignant mixed																									
Mandibular, lymphoma malignant undifferentiated cell type								X																	
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant lymphocytic																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant histiocytic																									
Pancreatic, lymphoma malignant lymphocytic																									
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant lymphocytic																									
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed											X														
Lymphoma malignant undifferentiated cell type								X																	
Thymus	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	M	M	M	+	+	+	+	+	+	+	M	+	M	M	M	M	M	M	M	M	+	M
Adenocarcinoma																									
Skin	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma											X														
Subcutaneous tissue, lymphoma malignant lymphocytic																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma			X																						
Alveolar/bronchiolar carcinoma, metastatic, lung			X																						
Lymphoma malignant histiocytic				X																					
Lymphoma malignant mixed																									
Nose	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear													+												
Schwannoma malignant													X												
Eye																									
Harderian gland							+	+	+	+	+	+			+	+	+	+	+		+			+	
Adenoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic				X																					
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed											X														
Urinary bladder	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									

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	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	154	155	161	162	163	164	165	172	173	174	175	181	182	183	184	185	191	192	193	194	195	201	203	204	205	
HEMATOPOIETIC SYSTEM																										
Blood	+			+					+								+	+		+				+	+	13
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen				X																						1
Lymphoma malignant lymphocytic																									X	1
Lymphoma malignant mixed																	X									2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lumbar, lymphoma malig histiocytic																										1
Lumbar, lymphoma malig lymphocytic																				X						1
Lumbar, mediastinal, mandibular, lymphoma malignant mixed																										1
Mandibular, lymphoma malignant histiocytic																								X		2
Mandibular, lymphoma malignant lymphocytic																				X					X	2
Mandibular, lymphoma malig mixed																	X									1
Mandibular, lymphoma malignant undifferentiated cell type																										1
Mediastinal, lymphoma malignant histiocytic																								X		1
Mediastinal, lymphoma malignant lymphocytic																									X	1
Mediastinal, lymphoma malig mixed																	X									1
Mesenteric, lymphoma malignant histiocytic																								X		1
Pancreatic, lymphoma malignant lymphocytic																				X						1
Pancreatic, lymphoma malignant mixed																	X									1
Renal, lymphoma malig lymphocytic																				X					X	2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																						1
Lymphoma malignant histiocytic																								X		1
Lymphoma malignant lymphocytic																									X	2
Lymphoma malignant mixed																	X									2
Lymphoma malignant undifferentiated cell type																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																				X					X	2
Lymphoma malignant mixed																	X									1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	+	M	M	+	M	M	M	M	M	M	M	+	M	M	+	M	+	M	+	+	+	M	+	19
Adenocarcinoma																	X									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sebaceous gland, adenoma																										1
Subcutaneous tissue, lymphoma malignant lymphocytic				X																						1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X										X						2
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant histiocytic																								X		2
Lymphoma malignant mixed																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																										1
Schwannoma malignant																										1
Eye														+												1
Harderian gland		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	35
Adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																								X		2
Lymphoma malignant lymphocytic				X																X					X	3
Lymphoma malignant mixed																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																				X						1
Lymphoma malignant mixed																	X									1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: LOW DOSE

WEEKS ON STUDY	0 3 9	0 7 3	0 7 5	0 7 8	0 8 5	0 8 8	0 8 9	0 9 3	0 9 7	0 9 9	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
CARCASS ID	3 4 4	4 0 3	3 3 1	3 5 1	3 5 3	4 0 5	3 9 1	3 8 5	3 4 5	3 5 2	3 1 1	3 1 2	3 1 3	3 1 4	3 1 5	3 2 1	3 2 2	3 2 3	3 2 4	3 2 5	3 3 2	3 3 3	3 3 4	3 3 5	3 4 1
ALIMENTARY SYSTEM																									
Intestine small																									
Liver				A		+														+				+	+
Hepatocellular adenoma																								X	X
Lymphoma malignant lymphocytic						X																			
Mesentery																									
Pharynx																				+					
Stomach											+										+	+	+	+	+
Forestomach, squamous papilloma											X														X
CARDIOVASCULAR SYSTEM																									
Heart						+																			
Lymphoma malignant lymphocytic						X																			
ENDOCRINE SYSTEM																									
Adrenal gland						+																			
Lymphoma malignant lymphocytic						X																			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary			+					+	+	+	+	+			+		+	+			+		+	+	
Granulosa cell tumor																									
Bilateral, lymphoma malignant lymphocytic										X															
Uterus				A			+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X						X									
Polyp stromal																X									
HEMATOPOIETIC SYSTEM																									
Lymph node				A		+				+			+		+	+	+		+						
Lymphoma malignant lymphocytic						X																			
Lumbar, lymphoma malignant lymphocytic										X						X									
Mesenteric, lymphoma malignant lymphocytic						X																			
Renal, lymphoma malignant lymphocytic						X																			
Spleen				A		+									+	+	+			+					
Lymphoma malignant lymphocytic						X										X									
Lymphoma malignant mixed																				X					
Thymus						+																			
Lymphoma malignant lymphocytic						X																			
INTEGUMENTARY SYSTEM																									
Mammary gland														+											
Basosquamous tumor benign														X											
Skin						+																			
Subcutaneous tissue, lymphoma malignant lymphocytic						X																			
MUSCULOSKELETAL SYSTEM																									
Bone										+			I												
Lymphoma malignant lymphocytic										X															
Skeletal muscle						+				+															
Lymphoma malignant lymphocytic						X				X															
NERVOUS SYSTEM																									
Spinal cord																									
RESPIRATORY SYSTEM																									
Lung																									
Alveolar/bronchiolar adenoma																									
SPECIAL SENSES SYSTEM																									
Harderian gland																				+					
URINARY SYSTEM																									
None																									

TABLE D2. 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	105	
CARCASS ID	342	343	354	355	361	362	363	364	365	371	372	373	374	375	381	382	383	384	392	393	394	395	401	402	404		TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																											
Intestine small							+														+					2	
Liver								+																		5	
Hepatocellular adenoma																										2	
Lymphoma malignant lymphocytic																										1	
Mesentery																								+		1	
Pharynx																										1	
Stomach	+	+			+								+	+	+					+					+	14	
Forestomach, squamous papilloma																				X						3	
CARDIOVASCULAR SYSTEM																											
Heart																										1	
Lymphoma malignant lymphocytic																										1	
ENDOCRINE SYSTEM																											
Adrenal gland																										1	
Lymphoma malignant lymphocytic																										1	
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ovary		+	+		+				+	+	+	+			+					+				+		22	
Granulosa cell tumor																								X		1	
Bilateral, lymphoma malignant lymphocytic																										1	
Uterus	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	40	
Lymphoma malignant lymphocytic																										2	
Polyp stromal													X													2	
HEMATOPOIETIC SYSTEM																											
Lymph node						+										+										9	
Lymphoma malignant lymphocytic																										1	
Lumbar lymphoma malig lymphocytic																										2	
Mesenteric, lymphoma malignant lymphocytic																										1	
Renal, lymphoma malig lymphocytic																										1	
Spleen					+			+				+														9	
Lymphoma malignant lymphocytic																										2	
Lymphoma malignant mixed								X				X														3	
Thymus																										1	
Lymphoma malignant lymphocytic																										1	
INTEGUMENTARY SYSTEM																											
Mammary gland																										1	
Basosquamous tumor benign																										1	
Skin																										1	
Subcutaneous tissue, lymphoma malignant lymphocytic																										1	
MUSCULOSKELETAL SYSTEM																											
Bone						+																				2	
Lymphoma malignant lymphocytic																										1	
Skeletal muscle																										2	
Lymphoma malignant lymphocytic																										2	
NERVOUS SYSTEM																											
Spinal cord						+																				1	
RESPIRATORY SYSTEM																											
Lung																									+	1	
Alveolar/bronchiolar adenoma																									X	1	
SPECIAL SENSES SYSTEM																											
Harderian gland										+																2	
URINARY SYSTEM																											
None																											

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL: HIGH DOSE

WEEKS ON STUDY	0 3 5	0 4 0	0 6 4	0 7 9	0 8 8	0 8 8	1 0 0	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	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
CARCASS ID	5 9 4	5 4 3	6 0 3	5 2 2	6 0 4	5 7 4	5 3 1	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 2 1	5 2 3	5 2 4	5 2 5	5 3 2	5 3 3	5 3 4	5 3 5	5 4 1	5 4 2	5 4 4	5 4 5	5 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Lymphoma malignant lymphocytic												X													
Mesentery	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, skin						X																			
Lymphoma malignant lymphocytic												X													
Sarcoma, metastatic, skin				X																					
Pancreas	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Salivary glands	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Stomach	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed																						X			
Tooth							+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin				X																					
Medulla, pheochromocytoma benign																			X						
Spindle cell, adenoma										X															
Islets, pancreatic	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	M	M	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	–	+	M
Pituitary gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Pars distalis, adenocarcinoma																									
Pars distalis, adenoma																									X
Pars intermedia, adenoma																									
Thyroid gland	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Choriocarcinoma			X																						
Cystadenoma																									
Granulosa cell tumor																									
Lymphoma malignant lymphocytic												X													
Perovarian tissue, lymphoma malignant mixed																						X			
Uterus	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic												X													
Lymphoma malignant mixed																						X			
Polyp stromal																									
Sarcoma					X																				
Sarcoma stromal											X														

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	101	104	104	104	104	104	104	104	104	104	104	104	104	104	
CARCASS ID	552	553	554	555	561	562	563	564	565	571	572	573	575	581	582	583	584	585	591	592	593	595	601	602	605	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																									1
Lymphoma malignant lymphocytic																										1
Mesentery	+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	48
Liposarcoma, metastatic, skin																										1
Lymphoma malignant lymphocytic																										1
Sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant undifferentiated cell type																							X			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Tooth	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymphoma malignant lymphocytic																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
Medulla, pheochromocytoma benign																				X						2
Spindle cell, adenoma																		X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																					X					1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	M	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Pars distalis, adenocarcinoma																	X									1
Pars distalis, adenoma					X					X																3
Pars intermedia, adenoma									X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Choriocarcinoma																										1
Cystadenoma																					X					1
Granulosa cell tumor																			X							1
Lymphoma malignant lymphocytic																										1
Periovarian tissue, lymphoma malignant mixed																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Polyp stromal										X																1
Sarcoma																										1
Sarcoma stromal																										1

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

WEEKS ON STUDY	035	040	064	079	088	088	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
CARCASS ID	594	543	603	522	604	574	531	511	512	513	514	515	521	523	524	525	532	533	534	535	541	542	544	545	551	
HEMATOPOIETIC SYSTEM																										
Blood								+						+						+		+				
Lymphoma malignant mixed																						X				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic												X														
Lymph node	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Sarcoma, metastatic, skin				X																						
Mandibular, lymphoma malignant lymphocytic												X														
Mandibular, lymphoma malignant undifferentiated cell type																										
Mediastinal, lymphoma malignant mixed																										
Mesenteric, lymphoma malignant undifferentiated cell type																										
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liposarcoma, metastatic, skin						X																				
Lymphoma malignant lymphocytic												X														
Lymphoma malignant mixed																						X				
Thymus	+	M	M	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant mixed																										
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	M	+	M	M	M	+	+	M	+	M	+	+	M	+	M	M	M	+	M	+	+	M	M	
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic												X														
Subcutaneous tissue, liposarcoma						X																				
Subcutaneous tissue, sarcoma				X																						
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle												+														
Lymphoma malignant lymphocytic												X														
NERVOUS SYSTEM																										
Brain	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic												X														
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, harderian gland							X																			
Alveolar/bronchiolar adenoma										X																
Liposarcoma, metastatic, skin						X																				
Lymphoma malignant lymphocytic												X														
Lymphoma malignant mixed																						X				
Nose	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, harderian gland							X																			
Lymphoma malignant lymphocytic												X														
Trachea	+	+	M	M	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Harderian gland							+	+	+	+	+	+		+	+	+	+		+	+	+	+	+		+	
Adenocarcinoma							X																			
Adenoma																			X							
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant lymphocytic												X														

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

WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL:
CARCASS ID	552	553	554	555	561	562	563	564	565	571	572	573	575	581	582	583	584	585	591	592	593	595	601	602	605	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood							+									+				+						7
Lymphoma malignant mixed																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, metastatic, skin																										1
Mandibular, lymphoma malignant lymphocytic																										1
Mandibular, lymphoma malignant undifferentiated cell type																							X			1
Mediastinal, lymphoma malig. mixed										X																1
Mesenteric, lymphoma malignant undifferentiated cell type																							X			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liposarcoma, metastatic, skin																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed										X																2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Lymphoma malignant mixed										X																1
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	M	29
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Subcutaneous tissue, liposarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, harderian gland																										1
Alveolar/bronchiolar adenoma												X														2
Liposarcoma, metastatic, skin																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, metastatic, harderian gland																										1
Lymphoma malignant lymphocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenocarcinoma																										1
Adenoma									X																	2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Control	5,000 ppm	10,000 ppm
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.2%	0.0%	6.8%
Terminal Rates (c)	1/45 (2%)	0/40 (0%)	2/43 (5%)
Day of First Observation	728		697
Life Table Tests (d)	P=0.173	P=0.523N	P=0.293
Logistic Regression Tests (d)	P=0.166	P=0 523N	P=0.287
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	(e) 1/1 (100%)	2/50 (4%)
Adjusted Rates (b)	6.4%		4.7%
Terminal Rates (c)	2/45 (4%)		2/43 (5%)
Day of First Observation	668		728
Life Table Test (d)			P=0.524N
Logistic Regression Test (d)			P=0.516N
Fisher Exact Test (d)			P=0.500N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	4/49 (8%)	(f)	3/48 (6%)
Adjusted Rates (b)	8.9%		7.0%
Terminal Rates (c)	4/45 (9%)		3/43 (7%)
Day of First Observation	728		728
Life Table Test (d)			P=0.525N
Logistic Regression Test (d)			P=0.525N
Fisher Exact Test (d)			P=0.512N
Pituitary Gland/Pars Distalis: Adenoma or Adenocarcinoma			
Overall Rates (a)	4/49 (8%)	(f)	4/48 (8%)
Adjusted Rates (b)	8.9%		9.3%
Terminal Rates (c)	4/45 (9%)		4/43 (9%)
Day of First Observation	728		728
Life Table Test (d)			P=0.619
Logistic Regression Test (d)			P=0.619
Fisher Exact Test (d)			P=0.631
Forestomach: Squamous Papilloma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	6.7%	7 5%	0.0%
Terminal Rates (c)	3/45 (7%)	3/40 (7%)	0/43 (0%)
Day of First Observation	728	728	
Life Table Tests (d)	P=0 113N	P=0.608	P=0.130N
Logistic Regression Tests (d)	P=0.113N	P=0 608	P=0.130N
Cochran-Armitage Trend Test	P=0 101N		
Fisher Exact Test (d)		P=0 661	P=0.121N
Forestomach: Squamous Papilloma or Squamous Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	8.9%	7.5%	0.0%
Terminal Rates (c)	4/45 (9%)	3/40 (7%)	0/43 (0%)
Day of First Observation	728	728	
Life Table Tests (d)	P=0.057N	P=0.564N	P=0.069N
Logistic Regression Tests (d)	P=0 057N	P=0 564N	P=0.069N
Cochran-Armitage Trend Test	P=0 049N		
Fisher Exact Test (d)		P=0 500N	P=0.059N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Control	5,000 ppm	10,000 ppm
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	12/50 (24%)	(e,g) 6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	26.1%	14.1%	9.3%
Terminal Rates (c)	11/45 (24%)	4/40 (10%)	4/43 (9%)
Day of First Observation	679	616	728
Life Table Tests (d)	P=0.025N	P=0.156N	P=0.036N
Logistic Regression Tests (d)	P=0.022N	P=0.118N	P=0.036N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.096N	P=0.027N

(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 tissue
(f) No tissues were examined for the 5,000-ppm group.
(g) Five livers and nine spleens were examined microscopically.

TABLE D4a. HISTORICAL INCIDENCE OF STOMACH SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Battelle Columbus Laboratories	
N-Phenyl-2-naphthylamine	1/49
l-Ascorbic acid	1/49
All others	0/244
TOTAL	(b) 2/342 (0.6%)
SD (c)	0.79%
Overall Historical Incidence	
TOTAL	(d) 18/1,994 (0.9%)
SD (c)	1.75%
Range (e)	
High	4/50
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Squamous cell papillomas
(c) Standard deviation
(d) Includes 13 squamous papillomas, 1 papilloma, NOS, 3 papillomatoses, and 1 squamous cell carcinoma
(e) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence at Battelle Columbus Laboratories		
Chlorobenzene	17/50	17/50
N-Phenyl-2-naphthylamine	24/50	24/50
C.I. Disperse Yellow 3	10/50	10/50
D & C Red No. 9	11/50	11/50
C.I. Solvent Yellow 14	9/50	12/50
Rotenone	9/49	9/49
l-Ascorbic acid	11/50	14/50
TOTAL	91/349 (26.1%)	97/349 (27.8%)
SD (b)	11.09%	10.36%
Range (c)		
High	24/50	24/50
Low	9/50	9/49
Overall Historical Incidence		
TOTAL	617/2,040 (30.2%)	636/2,040 (31.2%)
SD (b)	13.32%	12.83%
Range (c)		
High	37/50	38/50
Low	5/50	6/50

(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 D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(46)		(45)
Mucosa, cyst	1 (2%)		
Intestine small	(48)	(2)	(47)
Ileum, Peyer's patch, inflammation, acute, focal	1 (2%)		
Jejunum, Peyer's patch, hyperplasia, lymphoid, diffuse		1 (50%)	
Jejunum, Peyer's patch, hyperplasia, lymphoid, multifocal	1 (2%)		
Liver	(50)	(5)	(50)
Basophilic focus, multiple	1 (2%)		
Basophilic focus, single	2 (4%)		2 (4%)
Clear cell focus			1 (2%)
Hematopoietic cell proliferation, multifocal	1 (2%)		
Eosinophilic focus, single		1 (17%)	
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Inflammation, granulomatous, multifocal			1 (2%)
Inflammation, subacute, multifocal	1 (2%)		
Hepatocyte, hyperplasia, focal	1 (2%)		
Hepatocyte, inflammation, acute, focal	2 (4%)		
Hepatocyte, inflammation, necrotizing, subacute, multifocal	1 (2%)		
Hepatocyte, necrosis, acute, diffuse			1 (2%)
Hepatocyte, necrosis, acute, multifocal		1 (20%)	2 (4%)
Hepatocyte, nuclear alteration, focal			1 (2%)
Hepatocyte, vacuolization cytoplasmic, focal	1 (2%)	1 (20%)	
Kupffer cell, pigmentation, multifocal	1 (2%)		
Left lateral lobe, angiectasis, focal	1 (2%)		
Mesentery	(47)	(1)	(48)
Inflammation, acute, multifocal			1 (2%)
Inflammation, subacute, multifocal	1 (2%)		
Thrombus	1 (2%)		
Fat, necrosis, chronic, focal		1 (100%)	
Fat, necrosis, focal	1 (2%)		
Pancreas	(49)		(47)
Cyst, multifocal	1 (2%)		
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Acinus, atrophy, diffuse	1 (2%)		1 (2%)
Acinus, atrophy, focal	1 (2%)		1 (2%)
Acinus, atrophy, multifocal	1 (2%)		2 (4%)
Pharynx		(1)	
Palate, epithelium, hyperplasia		1 (100%)	
Salivary glands	(49)		(47)
Infiltration cellular, lymphocytic, focal			1 (2%)
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Stomach	(49)	(14)	(48)
Forestomach, erosion, focal	1 (2%)		
Forestomach, epithelium, hyperplasia, focal	10 (20%)	10 (20%)	4 (8%)
Mucosa, glandular, mineralization, diffuse	1 (2%)		
Tooth	(48)		(44)
Peridontal tissue, inflammation, acute, focal	1 (2%)		1 (2%)
Peridontal tissue, inflammation, granulomatous, focal	1 (2%)		
Peridontal tissue, inflammation, necrotizing, focal	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
CARDIOVASCULAR SYSTEM			
Heart	(50)	(1)	(50)
Myocardium, mineralization, multifocal	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(1)	(50)
Cortex, focal cellular change	3 (6%)		
Cortex, hyperplasia, focal	2 (4%)		
Medulla, hyperplasia, focal	2 (4%)		
Medulla, hypertrophy	1 (2%)		
Spindle cell, hyperplasia, diffuse	45 (92%)		47 (94%)
Spindle cell, hyperplasia, multifocal	1 (2%)		1 (2%)
Subcapsular, cyst	1 (2%)		
Parathyroid gland	(39)		(38)
Cyst	1 (3%)		
Hyperplasia, focal	1 (3%)		
Pituitary gland	(49)		(48)
Pars distalis, angiectasis, focal	1 (2%)		1 (2%)
Pars distalis, cyst			1 (2%)
Pars distalis, hyperplasia, focal	3 (6%)		3 (6%)
Pars distalis, hyperplasia, multifocal	3 (6%)		1 (2%)
Pars intermedia, hyperplasia, focal	2 (4%)		
Thyroid gland	(49)		(47)
Ectopic tissue	1 (2%)		
Follicle, cyst			2 (4%)
Follicle, cyst, multiple	1 (2%)		1 (2%)
Follicle, inflammation, granulomatous, focal			1 (2%)
Follicle, inflammation, subacute, multifocal			1 (2%)
Follicular cell, hyperplasia, cystic, focal			1 (2%)
Follicular cell, hyperplasia, multifocal	1 (2%)		3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(48)	(22)	(48)
Angiectasis, diffuse	1 (2%)		
Cyst	1 (2%)		
Hyperplasia, focal			1 (2%)
Bilateral, abscess, chronic active, multifocal	1 (2%)	1 (5%)	
Bilateral, periovarian tissue, cyst	1 (2%)	2 (9%)	2 (4%)
Follicle, cyst	2 (4%)	2 (9%)	5 (10%)
Left, abscess, chronic, focal		2 (9%)	
Left, periovarian tissue, cyst	3 (6%)	4 (18%)	3 (6%)
Left, follicle, cyst	2 (4%)	1 (5%)	1 (2%)
Periovarian tissue, cyst	1 (2%)	3 (14%)	5 (10%)
Right, abscess, chronic active, single		1 (5%)	
Right, periovarian tissue, cyst	4 (8%)	6 (27%)	2 (4%)
Right, follicle, cyst	1 (2%)	1 (5%)	
Uterus	(49)	(40)	(49)
Hyperplasia, cystic, glandular, diffuse			1 (2%)
Endometrium, angiectasis			1 (2%)
Endometrium, angiectasis, focal	1 (2%)		
Endometrium, hyperplasia, cystic, glandular, diffuse	48 (98%)	38 (95%)	44 (90%)
Endometrium, inflammation, suppurative, focal		1 (3%)	
Endometrium, metaplasia, squamous	1 (2%)		1 (2%)
Lumen, dilatation	3 (6%)		1 (2%)
Lumen, dilatation, diffuse	1 (2%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)		(50)
Femoral, hyperplasia, neutrophil, diffuse			1 (2%)
Lymph node	(48)	(9)	(46)
Bronchial, hyperplasia, lymphoid, diffuse	1 (2%)		
Lumbar, hyperplasia, lymphoid, diffuse		1 (11%)	
Lumbar, sinus, ectasia, focal	1 (2%)		
Mandibular, hyperplasia, lymphoid, diffuse			1 (2%)
Mediastinal, hyperplasia, lymphoid, diffuse			1 (2%)
Mediastinal, pigmentation, diffuse	1 (2%)		
Mesenteric, angiectasis, diffuse	5 (10%)		
Mesenteric, angiectasis, multifocal		1 (11%)	
Mesenteric, hyperplasia, lymphoid, diffuse		1 (11%)	
Renal, hyperplasia, lymphoid, diffuse		1 (11%)	1 (2%)
Spleen	(49)	(9)	(49)
Inflammation, chronic		1 (11%)	
Capsule, inflammation, acute, diffuse			1 (2%)
Lymphoid follicle, depletion lymphoid, diffuse	2 (4%)		1 (2%)
Lymphoid follicle, hyperplasia, lymphoid	1 (2%)		
Lymphoid follicle, hyperplasia, lymphoid, diffuse	2 (4%)	1 (11%)	4 (8%)
Lymphoid follicle, hyperplasia, lymphoid, multifocal	1 (2%)		1 (2%)
Red pulp, angiectasis, multifocal	1 (2%)		
Red pulp, hematopoietic cell proliferation, diffuse	4 (8%)	2 (22%)	2 (4%)
Thymus	(47)	(1)	(42)
Atrophy, diffuse	1 (2%)		
Depletion lymphoid, diffuse	2 (4%)		1 (2%)
Medulla, hyperplasia, lymphoid, diffuse			2 (5%)
Thymocyte, necrosis, acute, diffuse			1 (2%)
INTEGUMENTARY SYSTEM			
Skin	(48)	(1)	(49)
Face, subcutaneous tissue, inflammation, granulomatous, focal	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(2)	(50)
Cranium, myelofibrosis			2 (4%)
Cranium, myelofibrosis, focal			1 (2%)
Cranium, myelofibrosis, multifocal	1 (2%)		1 (2%)
Cranium, femur, myelofibrosis, diffuse			2 (4%)
Cranium, femur, myelofibrosis, multifocal			7 (14%)
Femur, myelofibrosis, diffuse	2 (4%)		1 (2%)
Femur, myelofibrosis, focal	4 (8%)		5 (10%)
Femur, myelofibrosis, multifocal	19 (38%)		12 (24%)
Vertebra, myelofibrosis, multifocal		1 (50%)	
NERVOUS SYSTEM			
Brain	(50)		(48)
Compression, focal	1 (2%)		1 (2%)
Meninges, infiltration cellular, lymphocytic, multifocal	3 (6%)		1 (2%)
Thalamus, mineralization	4 (8%)		3 (6%)
Third ventricle, infiltration cellular, lymphocytic, multifocal			1 (2%)
Spinal cord		(1)	
Thoracic, hemorrhage, acute, focal		1 (100%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL (Continued)

	Untreated Control	Low Dose	High Dose
RESPIRATORY SYSTEM			
Lung	(50)	(1)	(50)
Infiltration cellular, lymphocytic, multifocal	1 (2%)		1 (2%)
Inflammation, granulomatous, focal	1 (2%)		
Inflammation, subacute, focal	1 (2%)		
Alveolar epithelium, hyperplasia, focal	3 (6%)		3 (6%)
Interstitium, inflammation, subacute, focal			1 (2%)
Mediastinum, infiltration cellular, lymphocytic, multifocal	1 (2%)		
Vein, intima, mineralization, focal	1 (2%)		
Nose	(48)		(44)
Mucosa, inflammation, acute, multifocal	1 (2%)		
Submucosa, glands, ectasia, multifocal	1 (2%)		
SPECIAL SENSES SYSTEM			
Eye	(1)		
Developmental malformation	1 (100%)		
Harderian gland	(35)	(2)	(41)
Hyperplasia, focal	1 (3%)		1 (2%)
Infiltration cellular, lymphocytic, multifocal			1 (2%)
URINARY SYSTEM			
Kidney	(49)		(50)
Infiltration cellular, lymphocytic, multifocal			4 (8%)
Capsule, inflammation, subacute, diffuse			1 (2%)
Capsule, inflammation, subacute, multifocal	1 (2%)		
Cortex, infarct, chronic	1 (2%)		
Cortex, metaplasia, osseous, focal	1 (2%)		
membranoproliferative, subacute, diffuse			1 (2%)
Glomerulus, inflammation, proliferative, diffuse	1 (2%)		
Interstitial tissue, inflammation, multifocal			1 (2%)
Renal tubule, casts protein, diffuse	1 (2%)		
Renal tubule, cytoplasmic alteration, diffuse	1 (2%)		
Renal tubule, cytoplasmic alteration, multifocal	1 (2%)		
Renal tubule, degeneration	1 (2%)		
Renal tubule, degeneration, diffuse	1 (2%)		
Renal tubule, inflammation, necrotizing, subacute, multifocal			1 (2%)
Renal tubule, necrosis, acute, multifocal			1 (2%)
Renal tubule, pigmentation, diffuse			1 (2%)
Renal tubule, regeneration, focal	3 (6%)		
Renal tubule, regeneration, multifocal	2 (4%)		7 (14%)
Urinary bladder	(48)		(47)
Serosa, inflammation, acute, multifocal			1 (2%)
Submucosa, infiltration cellular, lymphocytic, multifocal			2 (4%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

		PAGE
TABLE E1	MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL	167

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 and 15 F344/N rats 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 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 was 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
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (6,12,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV(6 mo) Sendai (18 mo)	MHV (mouse hepatitis virus) (12,18,24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,12,24 mo)	RCV (rat coronavirus) Sendai (18 mo)	

II. Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	2/10	Reo 3
12	3/7	MHV
	3/7	GDVII
	2/7	Reo 3
18	3/10	Reo 3
	2/10	MHV
24	--	None positive

(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 RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF 2,4-DICHLOROPHENOL

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TABLE F1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	15	157	15	157	478	15	153	980
5	17	256	17	253	336	17	240	708
10	18	309	18	302	298	18	291	619
13	17	326	17	321	265	17	310	548
18	15	359	15	351	214	15	335	448
22	16	387	15	375	200	15	360	417
27	14	402	14	385	182	15	368	408
31	18	420	18	403	223	17	384	443
36	16	433	15	412	182	15	395	380
41	17	441	17	422	201	16	404	396
45	20	453	16	432	185	16	412	388
50	17	459	16	442	181	16	416	385
54	17	464	16	444	180	17	423	402
58	18	467	16	445	180	17	427	398
63	17	470	17	451	188	17	428	397
68	16	469	16	454	176	16	424	377
72	17	468	14	452	155	15	421	356
76	16	469	16	451	177	16	425	376
81	18	465	17	451	188	16	425	376
85	16	469	15	439	171	15	419	358
89	16	466	14	448	156	14	415	337
93	16	464	14	443	158	15	421	356
97	14	456	12	433	139	13	417	312
101	18	443	18	422	213	16	409	391
Mean	16.6	416	15.8	400	209	15.8	380	440
SD (c)	1.4		1.5		73	1.1		146
CV (d)	8.4		9.5		34.9	7.0		33.2

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of 2,4-dichlorophenol consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	14	123	13	123	264	14	123	569
5	13	167	13	163	199	13	163	399
10	13	193	13	189	172	12	188	319
13	10	199	10	195	128	10	188	266
18	12	210	10	206	121	10	199	251
22	11	222	10	216	116	10	211	237
27	10	231	10	231	108	9	221	204
31	12	231	11	228	121	11	218	252
36	11	239	11	233	118	11	223	247
41	12	244	12	241	124	11	228	241
45	12	251	11	243	113	10	229	218
50	11	257	11	248	111	10	231	216
54	11	263	11	253	109	11	240	229
58	12	271	11	261	105	11	244	225
63	13	281	12	268	112	12	250	240
68	12	289	12	277	108	12	254	236
72	12	295	11	280	98	11	262	210
76	12	301	11	284	97	11	268	205
81	15	312	16	297	135	14	275	255
85	11	314	11	299	92	11	281	196
89	12	322	13	308	106	12	288	208
93	13	329	12	316	95	12	288	208
97	10	332	10	319	78	9	304	148
101	14	331	13	323	101	14	301	233
Mean	12.0	259	11.6	250	122	11.3	237	251
SD (c)	1.3		1.4		39	1.4		82
CV (d)	10.8		12.1		32.0	12.4		32.7

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of 2,4-dichlorophenol consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	8.4	24.3	8.4	23.6	1,780	7.0	24.4	2,869
5	7.3	29.0	6.2	28.6	1,084	5.8	28.7	2,021
10	8.0	31.6	6.6	31.2	1,058	5.8	31.4	1,847
13	3.1	32.3	3.5	31.9	549	3.1	31.1	997
17	3.3	32.1	3.5	31.7	552	3.1	32.2	963
21	7.3	33.7	6.9	34.3	1,006	5.2	34.2	1,520
25	6.6	34.2	6.6	34.0	971	4.2	33.2	1,265
30	5.9	36.7	6.7	36.0	931	5.5	35.6	1,545
34	5.2	37.8	5.4	37.2	726	4.5	36.0	1,250
38	5.1	38.4	5.0	38.3	653	3.4	35.4	960
43	5.5	38.3	4.7	38.1	617	4.0	36.2	1,105
47	4.8	38.0	4.7	38.7	607	4.1	34.6	1,185
51	5.2	39.9	4.8	39.2	612	3.9	37.5	1,040
56	5.3	39.1	5.0	38.0	658	3.8	36.0	1,056
61	5.8	40.2	5.5	38.1	722	4.5	38.3	1,175
66	5.4	39.3	5.1	38.0	671	4.4	38.1	1,155
70	6.4	38.7	6.3	38.2	825	4.4	38.4	1,146
74	6.4	39.7	6.5	38.6	842	4.5	37.7	1,194
78	5.3	39.5	5.6	38.0	737	4.1	37.4	1,096
82	5.9	39.1	5.2	37.4	695	4.1	36.0	1,139
86	4.9	37.2	5.1	38.0	671	5.5	36.4	1,511
90	6.8	39.3	5.5	38.0	724	4.7	38.2	1,230
95	5.0	39.1	4.9	37.3	657	4.3	36.8	1,168
99	5.9	37.7	5.5	37.2	739	4.6	37.4	1,230
Mean	5.8	36.5	5.6	35.8	795	4.5	35.0	1,319
SD (c)	1.3		1.1		260	0.9		422
CV (d)	22.4		19.6		32.7	20.0		32.0

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of 2,4-dichlorophenol consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF 2,4-DICHLOROPHENOL

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	7.8	18.6	9.1	18.2	1,250	8.6	18.3	2,350
5	7.2	22.2	6.8	21.1	806	7.0	20.9	1,675
10	8.4	23.7	7.7	22.8	844	7.0	22.9	1,528
13	2.1	24.1	2.8	23.5	298	3.2	23.6	678
17	2.3	24.3	3.0	24.0	313	2.2	23.4	470
21	6.1	26.6	6.8	26.2	649	6.6	24.6	1,341
25	6.0	28.1	4.9	27.3	449	4.3	25.2	853
30	6.6	29.7	5.0	28.5	439	5.4	27.4	985
34	5.0	31.2	4.3	29.4	366	4.0	27.7	722
38	4.0	31.6	4.1	30.1	341	3.4	28.3	601
43	4.6	33.2	3.4	30.4	280	3.5	28.9	606
47	4.6	34.5	4.1	32.5	315	4.3	29.4	731
51	4.5	35.9	4.8	33.1	363	4.3	30.9	696
56	4.9	35.1	5.5	33.3	413	4.7	30.7	765
61	6.6	36.5	5.1	33.0	386	4.0	32.1	623
66	4.9	38.2	4.1	34.1	301	3.6	31.6	570
70	6.2	36.7	5.9	34.5	428	3.7	31.6	585
74	6.0	36.8	4.8	34.6	347	4.0	31.9	627
78	4.8	38.2	3.8	35.7	266	3.1	31.6	491
82	4.8	39.4	4.8	36.5	329	3.0	32.5	462
86	5.0	40.3	4.8	37.6	319	3.9	32.9	593
90	4.9	40.4	4.8	37.7	318	4.7	33.8	695
95	3.7	41.1	3.7	39.0	237	3.4	33.8	503
99	4.5	42.3	4.2	39.4	266	3.2	34.3	466
Mean	5.2	32.9	4.9	30.9	430	4.4	28.7	817
SD (c)	1.5		1.5		235	1.5		460
CV (d)	28.8		30.6		54.7	34.1		56.3

(a) Average grams of feed removed from feeder per animal per day. Not corrected for scatter.
(b) Estimated milligrams of 2,4-dichlorophenol consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX G

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

Pelleted Diet: December 1980 to January 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 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 (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.80 ± 2.0	14.0-21.0	(b) 23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.25 ± 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 ± 0.06	0.88-1.10	24
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured during 1983-85.
(b) One batch (7/22/81) net analyzed for thiamine

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.17	<0.29-1.06	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.00 ± 0.74	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
Nitrite nitrogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
BHA (ppm) (d)	6.68 ± 4.95	<0.4-17.0	24
BHT (ppm) (d)	3.45 ± 2.56	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	40,557 ± 29,431	4,900-88,000	23
Aerobic plate count (CFU/g) (f)	77,617 ± 183,824	4,900-930,000	24
Coliform (MPN/g) (g)	16.6 ± 22.9	<3-93	22
Coliform (MPN/g) (h)	80.2 ± 236.3	<3-1,100	24
E. coli (MPN/g) (i)	<3		24
Total nitrosamines (ppb) (j,k)	4.63 ± 4.19	0.8-18.5	21
Total nitrosamines (ppb) (j,l)	27.15 ± 64.35	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (j,k)	3.43 ± 3.96	0.8-16.5	21
N-Nitrosodimethylamine (ppb) (j,l)	25.71 ± 64.90	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
Pesticides (ppm)			
α-BHC (a,m)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (n)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (n)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) Mean, standard deviation, and range exclude one high value of 930,000 obtained for the batch produced on 12/22/82 (CFU = colony forming unit).
(f) Mean, standard deviation, and range include the high value listed in footnote (e).
(g) Mean, standard deviation, and range exclude one high value of 1,100 obtained for the batch produced on 12/16/80 and one high value of 460 obtained for the batch produced on 9/23/82 (MPN = most probable number).
(h) Mean, standard deviation, and range include the high values listed in footnote (g).
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(o) Thirteen batches contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and the draft NTP Technical Report No. 353 for the 2-year studies of 2,4-dichlorophenol in F344/N rats and B6C3F$_1$ mice were audited for the National Institute of Environmental Health Sciences at the National Toxicology Program (NTP) Archives in September and October 1987 by Argus Research Laboratories, Inc. The audit included review of:

(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, correlations of masses or clinical signs recorded at the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory, and wet tissues from a random 20% sample of animals from each study group 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 table to verify incorporation of changes into the final tables.
(9) Correlation between the data, results, and procedures for the 2-year studies presented in the preliminary draft Technical Report and the records available at the NTP Archives.

Review of the toxicology records and data revealed no instances that would affect the validity of these studies. In a few instances (3/18 rats and 18/76 mice), the clinical observation records and the individual animal necropsy records differed for the dates and/or disposition at death of animals that died before the end of the studies. A small number of masses apparently observed clinically (5 in the rat studies and 19 in the mouse studies) were not addressed among the gross observations recorded at necropsy or among the microscopic diagnoses; for the most part, these were small, hard lumps in the region of the penis. Audits of the analytical chemistry data and the pathology specimens revealed no findings that would affect the interpretation of the data.

Full details about these and other audit findings are presented in the audit reports. In conclusion, the data and results presented in the draft Technical Report for the 2-year exposure studies of 2,4-dichlorophenol are supported by the records at the NTP Archives.