NATIONAL TOXICOLOGY PROGRAM
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No. 319

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 1,4-DICHLOROBENZENE

(CAS NO. 106-46-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

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

January 1987

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be 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 Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

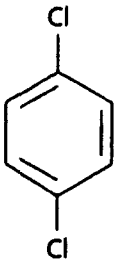
Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

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

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

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

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



1,4-DICHLOROBENZENE

CAS No. 106-46-7

$C_6H_4Cl_2$ Molecular weight: 147

Synonyms: *p*-Dichlorobenzene; *para*-Dichlorobenzene; *para*-Chlorophenyl chloride

ABSTRACT

1,4-Dichlorobenzene is commonly used as a space deodorant in toilets and for moth control. Because of its extensive production and use and the absence of carcinogenicity data, carcinogenesis studies were conducted by administering 1,4-dichlorobenzene (greater than 99% pure) in corn oil by gavage (5 days per week) to male F344/N rats at doses of 0, 150, or 300 mg/kg and to female F344/N rats and male and female B6C3F$_1$ mice at doses of 0, 300, or 600 mg/kg per day for 2 years (50 animals per group). Fourteen-day and 13-week studies were performed to characterize the toxicity, identify affected sites, and set doses for the 2-year studies. Clinical chemistry and hematologic studies were performed during the 13-week studies to assess the effects of 1,4-dichlorobenzene on the liver, kidney, and hematopoietic system and to assess whether the compound produced hepatic porphyria.

Two 13-week studies were performed in rats. In the first study, rats were dosed with 300-1,500 mg/kg 1,4-dichlorobenzene. Because histologic changes were observed in the kidney of male rats at all doses, a second 13-week study was performed at doses of 38-600 mg/kg. In the 13-week studies, survival was decreased in groups of male rats given 1,200 or 1,500 mg/kg and in female rats given 1,500 mg/kg. Weight gain was decreased in male rats receiving doses of 300 mg/kg or more and in female rats given doses of 1,200 or 1,500 mg/kg. Doses of 1,200 or 1,500 mg/kg produced degeneration and necrosis of hepatocytes, hypoplasia of the bone marrow, lymphoid depletion of the spleen and thymus, and epithelial necrosis of the nasal turbinates in male and female rats. Renal tubular cell degeneration was observed in male rats receiving 300 mg/kg or more in the first study, but only slight changes were seen at 300 mg/kg in the second study. Liver weight to brain weight ratios were increased at 900 mg/kg or more for both male and female rats. The kidney weight to brain weight ratio was increased in male rats receiving doses of 600 mg/kg or more.

Administration of 1,4-dichlorobenzene to rats for 13 weeks produced slight but statistically significant decreases in the hematocrit, red blood cell count, and hemoglobin level in all males receiving doses of 300-1,200 mg/kg. No clear hematologic changes were observed in female rats. 1,4-Dichlorobenzene produced minimal changes in clinical chemistry parameters in the 13-week studies. Serum cholesterol levels were increased by doses of 600 mg/kg or more in male rats and 900 mg/kg or more in female rats. Serum triglycerides were reduced by doses of 300 mg/kg or more in male rats. The blood urea nitrogen level was increased slightly in male rats dosed with 900 mg/kg or more.

Urinary porphyrins were increased slightly in male rats administered 1,200 or 1,500 mg/kg and female rats receiving 1,200 mg/kg. However, these increases were modest and indicative of a mild porphyrinuria rather than hepatic porphyria. Liver porphyrins were not increased at any dose.

Two 13-week studies were performed in mice. The doses selected for the first study were 600-1,800 mg/kg. Survival was decreased in male and female mice receiving doses of 1,500 mg/kg or more, and body weight gain was decreased at all doses. Hepatocellular degeneration was observed in both sexes at all doses, and the liver weight to brain weight ratio was increased at doses of 900 mg/kg or more. Serum cholesterol levels were increased in male mice at doses of 900 mg/kg or more, whereas serum protein and triglycerides were increased at doses of 1,500 mg/kg or more. These relatively modest clinical chemistry changes probably reflect the hepatic effects of this compound. The white blood cell count was reduced significantly in male mice receiving doses of 600 mg/kg or more and female mice receiving 1,000 mg/kg or more, but this effect was not dramatic. Hepatic porphyria was not found in mice at any dose in the 13-week study. Because hepatic effects were seen in all dose groups in the first study, a second 13-week study was performed at doses of 85-900 mg/kg. In this study, hepatocellular cytomegaly was observed in male and female mice at doses of 675 mg/kg or more but not at 338 mg/kg. Renal damage was not observed in mice in either 13-week study.

Based on the histopathologic findings in the kidney of male rats and in the liver of both sexes of rats and mice in the 13-week studies, the doses selected for the 2-year studies were 150 and 300 mg/kg for male rats and 300 and 600 mg/kg for female rats and male and female mice. In the 2-year studies, survival of female rats and of both sexes of mice was comparable to that of vehicle controls; survival of high dose male rats was significantly lower than that of the vehicle controls (vehicle control, 32/50; low dose, 31/50; high dose, 20/50). Mean body weights of high dose male rats were 5%-8% lower than those of vehicle controls after week 38, and those of high dose female rats were 5%-7% lower than those of vehicle controls after week 55. Mean body weights of mice dosed with 1,4-dichlorobenzene were comparable to those of vehicle controls throughout the studies.

Administration of 1,4-dichlorobenzene to male rats increased the average severity of nephropathy and caused epithelial hyperplasia of the renal pelvis (1/50; 30/50; 31/50), mineralization of the collecting tubules in the renal medulla (4/50; 46/50; 47/50), and focal hyperplasia of renal tubular epithelium (0/50; 1/50; 9/50). There were increased incidences of nephropathy in both low and high dose female rats compared with vehicle controls (21/49; 32/50; 41/49). 1,4-Dichlorobenzene produced a dose-related increase in the incidence of tubular cell adenocarcinomas of the kidney in male rats (1/50; 3/50; 7/50); one tubular cell adenoma was observed in a high dose male rat. These malignant tumors are uncommon in male F344/N rats. They have been diagnosed in only 4/1,098 (0.4%) corn oil gavage controls in previous NTP studies. There were no tubular cell tumors in dosed or vehicle control female rats. There was a marginal increase in the incidence of mononuclear cell leukemia in dosed male rats compared with that in vehicle controls (5/50; 7/50; 11/50).

1,4-Dichlorobenzene increased the incidences of nonneoplastic liver lesions in male and female mice, including alteration in cell size (cytomegaly and karyomegaly), hepatocellular degeneration, and individual cell necrosis. 1,4-Dichlorobenzene also increased the incidences of nephropathy in male mice and renal tubular regeneration in female mice. 1,4-Dichlorobenzene increased the incidences of hepatocellular carcinomas in high dose male (14/50; 11/49; 32/50) and female (5/50; 5/48; 19/50) mice and hepatocellular adenomas in dosed male (5/50; 13/49; 16/50) and high dose female (10/50; 6/48; 21/50) mice. Hepatoblastomas were observed in four high dose male mice but not in vehicle controls. This rare tumor has not occurred in 1,091 male vehicle control mice in NTP studies. An increase in thyroid gland follicular cell hyperplasia was observed in dosed male mice (1/47; 4/48; 10/47), and there was a marginal positive trend in the incidence of follicular cell adenomas of the thyroid gland in female mice (0/48; 0/45; 3/46). Pheochromocytomas (benign or malignant, combined) of the adrenal gland occurred with a positive trend in dosed male mice, and the incidence in the high dose group was

significantly greater than in the vehicle controls (0/47; 2/48; 4/49). The incidence of adrenal gland medullary hyperplasia in male mice was 2/47, 4/48, and 4/49. Focal hyperplasia of the adrenal gland capsule was also observed in dosed male mice (11/47; 21/48; 28/49).

1,4-Dichlorobenzene was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without activation by Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when tested according to a preincubation protocol at concentrations up to 100 µg/plate. 1,4-Dichlorobenzene did not induce forward mutations in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of exogenous metabolic activation; however, the results were equivocal in this system in the presence of metabolic activation. 1,4-Dichlorobenzene did not produce an increase in sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in culture with or without exogenous metabolic activation. No increase in micronucleated cells was seen in erythrocytes of mice from the first 13-week studies.

An audit of the experimental data was conducted for the 2-year studies of 1,4-dichlorobenzene. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, 1,4-dichlorobenzene produced *clear evidence of carcinogenicity** for male F344/N rats, as shown by an increased incidence of renal tubular cell adenocarcinomas. There was *no evidence of carcinogenicity* for female F344/N rats receiving doses of 300 or 600 mg/kg. There was *clear evidence of carcinogenicity* for both male and female B6C3F$_1$ mice, as shown by increased incidences of hepatocellular carcinomas and hepatocellular adenomas. Marginal increases were observed in the incidences of pheochromocytomas of the adrenal gland in male mice. Nonneoplastic effects in the kidney of male and female rats, in the liver of male and female mice, and in the thyroid gland and adrenal gland of male mice were also associated with the administration of 1,4-dichlorobenzene.

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*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

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APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 1,4-dichlorobenzene on March 26, 1986, 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 1,4-DICHLOROBENZENE

On March 26, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of 1,4-dichlorobenzene 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, Research Triangle Park, North Carolina.

Dr. J. Goldstein, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenicity for male rats, no evidence of carcinogenicity for female rats, clear evidence of carcinogenicity for male and female mice).

Dr. Swenberg, a principal reviewer, agreed with the conclusion in female rats. He proposed that the conclusions in male rats and male and female mice be changed to some evidence of carcinogenicity based on: (1) occurrence of tumors only in tissues where there was considerable toxicity, (2) lack of genotoxicity in a battery of short-term tests, and (3) a negative finding for carcinogenicity in previous inhalation studies. Dr. S. Eustis, NIEHS, commented that although the incidence of nonneoplastic lesions in mice was great, the toxicity (single cell necrosis) was not severe but generally minimal to mild. Dr. Swenberg thought that the inhalation route would have been more appropriate than the gavage route, since it is the predominant route of human exposure. Dr. Goldstein responded that oral administration was a valid route, since the chemical is found in drinking water and also in many waste dumps. Regarding the negative findings in the previous inhalation studies, she reported that the exposure period in rats was only 76 weeks versus 102 weeks in the present studies, and the mice in the earlier inhalation studies suffered from high early mortality because of fighting and a respiratory infection. Therefore, exposures were terminated at 61 weeks and surviving mice were killed at 51-61 weeks (males) or 75-76 weeks (females).

As a second principal reviewer, Dr. Crowley agreed with the conclusions as written. He thought that based on the short-term studies, the top dose in male rats in the 2-year study was probably too high.

As a third principal reviewer, Dr. Hooper agreed with the conclusions as written. He said that the conclusions in mice were supported by the finding of rare hepatoblastomas in high dose males. In view of the similarity of renal toxicity in male rats to that observed with other hydrocarbons, Dr. Hooper asked whether there was evidence of the role of the α-2-microglobulin in these effects. Dr. Eustis commented that although the accumulation of hyaline droplets in renal tubules (presumably α-2-microglobulin) is seen earlier than most of the renal lesions, there is no direct evidence for a cause-and-effect relationship between the protein and the later appearing lesions. Dr. Hooper suggested that inclusion of concentration levels of 1,4-dichlorobenzene in products for home use, such as mothballs, and for commercial use, such as toilet disinfectant, would be useful. Dr. Goldstein said that this information would be included if available.

In further discussion, Dr. Mirer cautioned against giving too much weight to results of the previous inhalation studies, since the protocols and other aspects of the studies were different from the NTP studies. With regard to the concomitant toxicity and tumors in the same organ, he stated that it would be departure from past practice for the Panel to lower the level of evidence because of concurrent toxicity. Dr. Swenberg said that after hearing clarifying remarks on liver tumors in mice and because of the rarity of the hepatoblastomas found in high dose male mice, he would agree that the level of evidence in male and female mice should remain clear evidence of carcinogenicity.

Dr. J. Barter, representing the Chlorobenzene Producers Association, made several comments on the Technical Report. He opined that the differences reported between the inhalation studies and the NTP oral studies were important and should not be overlooked. He noted that there was considerable scientific debate about the relevance of liver tumors in mice as predictive of human cancer in view of the high and variable spontaneous incidences of such tumors. Finally, he said that the Association believed that the cited number of humans occupationally exposed was seriously overestimated. Dr. J. Huff, NIEHS, mentioned that liver neoplasia was not uniformly high in mice; the background rates for male B6C3F$_1$ mice are high but female mice have a relatively low rate in comparison. He asked for more accurate information on occupational exposures if available. [See p. 14.]

Dr. Perera felt that too much attention was being given to other studies and that emphasis should be placed on the NTP studies being reviewed. Dr. Swenberg argued that the previous inhalation studies as well as information on apparent lack of genotoxicity of the chemical were relevant to determining the strength of evidence in the present studies.

Dr. Hooper moved that the Technical Report on 1,4-dichlorobenzene be accepted with the conclusions as written, clear evidence of carcinogenicity for male rats and male and female mice, and no evidence of carcinogenicity for female rats. Dr. Perera seconded the motion and it was approved by 10 affirmative votes to 1 negative vote (Dr. Swenberg).

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene is based on the first 13-week studies that began in July 1978 and ended in October 1978, the second 13-week studies that began in July 1979 and ended in September 1979, and the 2-year studies that began in May 1980 and ended in May 1982 at Battelle Columbus Laboratories.

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I. INTRODUCTION

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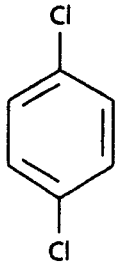

1,4-DICHLOROBENZENE

CAS No. 106-46-7

$C_6H_4Cl_2$ Molecular weight: 147

Synonyms: *p*-Dichlorobenzene; *para*-Dichlorobenzene; *para*-Chlorophenyl chloride

Use and Production

1,4-Dichlorobenzene is used primarily as a space deodorant (55%) and for moth control (35%) (IARC, 1982). Solid 1,4-dichlorobenzene is commonly used to mask odors in toilets. Other applications (10%) include use as an intermediate in organic syntheses. The most important synthetic product is the dye intermediate 2,5-dichloroaniline. 1,4-Dichlorobenzene is also used in the synthesis of polyphenylene sulfide resins that are used in the electronic and electrical industries. It is registered for use as an animal repellent.

The production of 1,4-dichlorobenzene was estimated to be 33 million kg in 1982 (USITC, 1983). No imports of 1,4-dichlorobenzene were reported in 1982 (U.S. Department of Commerce, 1983). U.S. exports of all dichlorobenzenes were reported to be 17 million kg in 1980 (U.S. Department of Commerce, 1981).

As reported in 1980, approximately 1 million workers in the United States are occupationally exposed to 1,4-dichlorobenzene, primarily via the inhalation route (USEPA, 1980a). According to one survey, approximately 821 workers were exposed to 1,4-dichlorobenzene during production, captive use, and shipment from producers (Hull & Co., report prepared for Chlorobenzene Producers Association, 1980). Levels of 42-4,350 mg/m^3 have been measured in various factory operations (USEPA, 1980a,b). The Occupational Safety and Health Administration has set 75 ppm (450 mg/m^3) as the highest acceptable time-weighted-average concentration for an 8-hour exposure in a 40-hour workweek (OSHA, 1980).

1,4-Dichlorobenzene has been measured in ambient air in a number of studies (Bozelli and Kebbekus, 1979; USEPA, 1980a). Values (up to 5 ppb) reported for urban areas were greater than those for rural areas. 1,4-Dichlorobenzene also has been reported in some samples of raw and finished drinking water in the United States (0.07-2 µg/liter) (USEPA, 1980b). Higher concentrations were reported in discharges of industrial and municipal sewage treatment plants (generally 2-12 µg/liter).

Morita and Ohi (1975) reported indoor concentrations of 1,4-dichlorobenzene from its use as a space deodorant or moth repellant of 1,700 µg/m^3 (283 ppb) (wardrobe), 315 µg/m^3 (52 ppb) (closet), and 105 µg/m^3 (18 ppb) (bedroom) compared with outdoor concentrations of 1.5-4.2 µ/m^3 in the Tokyo area.

Metabolism

The ability of animals to metabolize chlorinated benzenes decreases as the number of chlorine atoms increases (Matthews, 1982). The position of the chlorine atom on the benzene ring is also important. 1,4-Dichlorobenzene is metabolized

more slowly than 1,2-dichlorobenzene in both rabbits and rats (Azouz et al., 1955; Reid and Krishna, 1973). In rabbits, the major metabolites of 1,4-dichlorobenzene are 2,5-dichlorophenol and the sulfate and glucuronide conjugates of 2,5-dichlorophenol (Azouz et al., 1955). In contrast to other dichlorobenzenes, mercapturic acids and catechols were not found as metabolites in the rabbit.

Hawkins et al. (1980) compared tissue distribution and metabolism of 1,4-[^{14}C]dichlorobenzene after daily administration by the oral (250 mg/kg), subcutaneous (250 mg/kg), or inhalation (1,000 ppm for 3 hours per day) routes to adult female CFY (Sprague-Dawley derived) rats for 2-10 days. Tissue distribution and patterns of excretion were similar for the three routes. The concentration in the tissues was highest at 4-6 days, indicating a low potential for bioaccumulation. The highest concentration was in fat, followed in descending order by kidney, lung and liver, plasma, and muscle. The concentration in fat was generally at least 10-30 times the concentration in other tissues. Most of the radioactivity was excreted in the urine (91%-97%), only 2%-6% in feces, and little in expired air (0.2% after inhalation; 1% after oral and 6% after subcutaneous administration). The two major urinary metabolites were the sulfate (46%-54%) and the glucuronide conjugates (31%-34%) of 2,5-dichlorophenol. Two minor metabolites, a dihydroxydichlorobenzene and a mercapturic acid conjugate of 1,4-dichlorobenzene, were identified in acid hydrolysates of urine. In bile duct-cannulated animals, 49% of the excreted radioactivity was found in bile after an inhalation dose and 63% after an oral dose. A comparison of the amount excreted in feces versus bile indicates that enterohepatic circulation occurred in intact animals. In bile duct-cannulated animals dosed orally, 9% of the radioactivity was excreted in feces, indicating approximately 91% absorption. 2,5-Dichlorophenol glucuronide and an unidentified metabolite were the major metabolites found in bile. The unidentified metabolite was not found in urine or feces, indicating that it is reabsorbed in vivo. The disappearance of radioactivity from the various tissues was determined in animals killed at various times after daily administration for 10 days. Concentrations were highest within 8 hours of the last dose and declined rapidly thereafter. Tissue concentrations were approximately one-third the maximum value 24 hours after the last dose and were negligible after 5 days.

Kimura et al. (1979) administered single oral doses of 200 mg/kg nonradioactive 1,4-dichlorobenzene to male Wistar rats. Gas chromatographic determinations indicated that tissue concentrations of 1,4-dichlorobenzene reached a maximum 6-20 hours after administration and that the compound disappeared from the blood, liver, kidney, lung, heart, and brain by 48 hours. 1,4-Dichlorobenzene was still present in fat at 120 hours, but the concentration was only 2% of the peak values. The half-life in fat appeared to be approximately 24 hours. Two metabolites of 2,5-dichlorophenol (2,5-dichlorophenyl methyl sulfoxide and 2,5-dichlorophenyl methyl sulfone) were identified. The concentration of the methyl sulfoxide metabolite was highest in kidney, followed in descending order by blood, adipose tissue, and liver. The concentration of the dimethyl sulfone was highest in blood, followed in descending order by adipose tissue, kidney, and liver. The peak concentrations of both metabolites in blood were only 10% that of the parent compound; however, the dimethyl sulfone disappeared more slowly from blood than did the parent compound. Dimethyl sulfone concentrations peaked at 18-48 hours; the compound was still detectable in blood at 120 hours, although its concentration had decreased by approximately 90%. Both compounds were found in urine at very low concentrations (less than 0.03% of the total dose).

In humans, 1,4-dichlorobenzene is converted to 2,5-dichlorophenol and 2,5-dichlorohydroquinone (Hallowell, 1959; Pagnotto and Walkley, 1965). The phenol is excreted as the glucuronide and sulfate conjugates. 1,4-Dichlorobenzene has been reported in fat and plasma of humans in Japan and in plasma of humans in Louisiana (Morita, 1977). The mean concentration in 34 samples of human fat taken from residents in the Tokyo area was 2 ppm.

Chlorobenzene, bromobenzene, iodobenzene, and 1,2-dichlorobenzene bind covalently to liver protein and produce hepatic centrilobular necrosis when administered to rats (Reid and Krishna, 1973; Brodie et al., 1971). Phenobarbital

pretreatment enhances these effects, apparently by increasing metabolism by the hepatic cytochrome P-450 system that is responsible for the initial hydroxylation of chlorinated benzenes (Matthews, 1982). In contrast to mono- and 1,2-dichlorobenzene, 1,4-dichlorobenzene did not produce hepatic necrosis when injected into control or phenobarbital-dosed rats at similar doses (single doses of 0.5 mmol/kg) (Brodie et al., 1971; Reid and Krishna, 1973). Covalent binding of 1,4-dichlorobenzene to liver and lung protein was 90%-98% less than that of mono- or 1,2-dichlorobenzene (Reid et al., 1973; Reid and Krishna, 1973). 1,4-Dichlorobenzene was present at higher concentrations in the liver and was metabolized and disappeared from the tissues more slowly than did 1,2-dichlorobenzene. The lower rate of metabolism of 1,4-dichlorobenzene to reactive metabolites relative to mono- and 1,2-dichlorobenzene may explain the difference in the relative hepatotoxicity and the covalent binding of these chlorinated benzenes.

Acute Toxicity

Hollingsworth et al. (1956) reported that the LD_{50} value for 1,4-dichlorobenzene administered orally in olive oil to rats was greater than 1.0 g/kg but less than 4.0 g/kg. The LD_{50} value for guinea pigs was greater than 1,600 mg/kg but less than 2,800 mg/kg. Zupko and Edwards (1949) reported an LD_{50} value of 2.6 g/kg for 1,4-dichlorobenzene administered intraperitoneally to Wistar rats. Domenjoz (1946) reported an oral LD_{50} value of 2.95 g/kg in white mice. Irie et al. (1973) reported a subcutaneous LD_{50} value of 5.15 g/kg for mice. The effects of acute oral administration generally included increased lacrimation, salivation, and excitation followed by ataxia, dyspnea, and death from respiratory paralysis within 3 days. At necropsy, enlarged livers with necrosis and necrotic changes in the kidneys were observed. Eye and nose irritation, hemorrhage and edema of the lungs, renal and hepatic necrosis, and central nervous system depression were observed after inhalation (Hollingsworth et al., 1956).

Short-Term and Subchronic Toxicity

Zupko and Edwards (1949) administered a high dose of 1,4-dichlorobenzene by inhalation (calculated to be 100 mg/liter air) for 30 minutes per day for 30 days to rabbits and 20 minutes per day to Wistar rats (11-25 days). This dose caused narcosis in both species and some deaths. A decrease in granulocyte counts was reported in rats and rabbits; the counts returned to normal after cessation of exposure. Hemorrhagic areas in the lungs, edema of the lung tissue, and kidney damage (but little liver damage) were observed.

Hollingsworth et al. (1956) administered 1,4-dichlorobenzene in olive oil by gavage 5 days per week for 4 weeks to adult male rats (two per group; strain unspecified) at 10, 100, or 500 mg/kg. Animals were killed 1 day after the last dose. Necrosis of the centrilobular area of the liver, swelling and cloudiness in the renal tubular epithelium, and casts in the kidney were reported in rats administered 500 mg/kg per day. In a longer study, female white rats (10 per group) were administered 18.8, 188, or 376 mg/kg 1,4-dichlorobenzene in olive oil containing 5%-10% gum arabic emulsifier for a total of 138 doses in 192 days. 1,4-Dichlorobenzene at 188 mg/kg per day increased liver and kidney weights, and increases in kidney and liver weights and focal necrosis and slight cirrhosis of the liver were observed at 376 mg/kg. No hematologic changes or bone marrow abnormalities were observed. No effects were noted at 18.8 mg/kg.

Hollingsworth et al. (1956) administered 1,4-dichlorobenzene by gavage to rabbits at 500 mg/kg (5 days per week for 367 days or a total of 263 doses) or 1,000 mg/kg (92 doses over 219 days). At 500 mg/kg per day, enlargement of the liver and a few areas of necrosis were found, and animals exhibited weakness, tremors, and weight loss. At the higher dose, some deaths occurred. No hematologic changes were observed. Rats, rabbits, and guinea pigs were also exposed to 1,4-dichlorobenzene by inhalation. Inhalation at 96 ppm (7 hours per day, 5 days per week for 6-7 months) produced no effects in 10 female mice, 10 rats, 1 rabbit of each sex, 8 guinea pigs, or 1 female monkey. At 173 ppm (7 hours per day, 5 days per week for 16 days), exposure of rats (five per sex), guinea pigs (five per sex), and rabbits (one of each sex) did not affect growth or mortality but did increase liver and kidney weights of rats and decrease spleen weights of

male guinea pigs. Congestion and granular degeneration of the centrilobular areas of the liver were observed in female rats. Examination of the lung revealed some interstitial edema and congestion and alveolar hemorrhage and edema in male rats, female guinea pigs, and the female rabbit. At 341 ppm, 20 male rats, 8 male guinea pigs, 8 female guinea pigs, and 1 male and 1 female rabbit were exposed 7 hours per day, 5 days per week for 6 months. The only effects noted were increases in liver and kidney weights of male rats; cloudy swelling, fatty degeneration, and focal necrosis of the liver of male guinea pigs; and a slight depression of growth in male guinea pigs. At 798 ppm (8 hours per day, 20-69 exposures), deaths occurred in 2/19 male rats, 2/15 female rats, 2/16 male guinea pigs, 0/7 female guinea pigs, 3/8 male rabbits, and 1/8 female rabbits. Signs of toxicity included tremors, weakness, unconsciousness, and weight loss. Irritation of the lungs, including slight congestion and emphysema, were found in two rabbits. Microscopic examination of the liver revealed slight to moderate changes, including cloudy swelling and centrilobular necrosis. Cloudy swelling of the tubular epithelium of kidney of female rats also was observed.

Another chlorinated benzene, hexachlorobenzene, was responsible for an outbreak of porphyria cutanea tarda in approximately 3,000 people in Turkey from 1955 through 1959 (Cam and Nigogosyan, 1963). The amount of hexachlorobenzene ingested by individuals with this syndrome was estimated to be approximately 0.05-0.2 g per day for a relatively long period of time. Exposure began in 1954-1955, but many incidents were first noted in 1956. The signs of the disease included cutaneous lesions, neurologic manifestations, and excretion of large amounts of porphyrins in the urine. The porphyrinuria has been reproduced in rats (Ockner and Schmid, 1961). Rimington and Ziegler (1963) reported that large doses of a number of other chlorinated benzenes, including 1,4-dichlorobenzene (770 mg/kg per day for 5 days), also produced porphyrinuria in rats. However, the doses used in this study were quite large, and the increases in porphyrin excretion were modest compared with the large increases produced by short-term administration of hexachlorobenzene. Later work showed that, unlike hexachlorobenzene, which produces porphyria in female rats when administered for 3 months at dietary concentrations as low as 50 ppm (Carlson, 1977), neither 1,4-dichlorobenzene nor 1,2,4-trichlorobenzene produced hepatic porphyria at concentrations of 50-200 ppm. Moreover, pentachlorobenzene did not affect tissue or urinary porphyrins when administered in the diet for 6 months at doses as high as 1,000 ppm (Linder et al., 1980). Therefore, although hexachlorobenzene is clearly porphyrogenic in rats, there is little evidence that less chlorinated benzenes cause porphyria in this species.

The chlorinated benzenes, including 1,4-dichlorobenzene, induce hepatic drug-metabolizing enzymes and produce hypertrophy of the liver (Carlson and Tardiff, 1976; Goldstein et al., 1982). 1,4-Dichlorobenzene is less potent than many of the more highly chlorinated benzenes but is more potent than 1,2-dichlorobenzene. Hawkins et al. (1980) suggested that enzyme induction was probably responsible for the greater levels of 1,4-dichlorobenzene in tissues after 4-6 daily doses than after 10 daily doses.

Effects on Reproduction and Teratology

Hayes et al. (1985) studied the teratogenic potential of 1,2-dichlorobenzene and 1,4-dichlorobenzene in rabbits and 1,2-dichlorobenzene in rats. Groups of inseminated female F344 rats (30-32) or New Zealand white rabbits (28-30) were exposed by inhalation at 0, 100, 300, or 800 ppm 1,4-dichlorobenzene or 0, 100, 200, or 400 ppm 1,2-dichlorobenzene 6 hours per day on days 6-15 (rats) or days 6-18 (rabbits) of gestation. Both 1,2- and 1,4-dichlorobenzene produced a slight decrease in maternal weight gain of rabbits at the highest dose on days 6-8 of gestation; however, there was no effect on liver or kidney weights at the end of the study. In fetuses, the incidences of external, soft tissue, and skeletal alterations appeared similar in control and 1,4-dichlorobenzene-dosed rabbits. There was a significant increase in resorptions at 300 ppm but not at 800 ppm. Therefore, the investigators concluded that the increase at the 300-ppm dose was probably not compound related. 1,2-Dichlorobenzene also produced no effect on the number of pregnancies, litter size, or resorption rate. The incidence of major malformations was not

increased in any of the exposed groups compared with the controls.

In pregnant rats dosed with 1,2-dichlorobenzene, there was no effect on litter size, resorption, or fetal measurements (Hayes et al., 1985). The incidence of major malformations was not increased. There was a significant delay in the ossification of the vertebrae in the offspring of the 400-ppm group. The 400-ppm dose produced a transient decrease in weight gain in female rats on days 6-8 of gestation and produced a significant increase in liver weight at the end of the study, indicating that this dose produced slight maternal toxicity.

Hodge et al. (1977) (reviewed by Loeser and Litchfield, 1983) examined the teratogenic potential of 1,4-dichlorobenzene in pregnant rats (an SPF colony, Alderley Park, Wistar-derived strain, 32 per group). Exposure was by inhalation at 0, 75, 200, or 500 ppm for 6 hours per day for days 6-15 of gestation. In this study, it was concluded that 1,4-dichlorobenzene had no effect on implantations, resorptions, number of viable fetuses, corpora lutea, fetal weight, litter weight, or implantation efficiency. It was not embryotoxic, fetotoxic, or teratogenic in rats at these concentrations, and there was no effect on maternal weight gain. The results of these studies indicate that 1,4-dichlorobenzene is not teratogenic to rats or rabbits (Hayes et al., 1985; Hodge et al., 1977).

Carcinogenicity Studies

Groups of 76-79 male and female SPF rats (Alderley Park, Wistar-derived strain) were exposed by inhalation to 1,4-dichlorobenzene at 0, 75, or 500 ppm 5 hours per day 5 days per week for 76 weeks (Riley et al., 1980a, summarized by Loeser and Litchfield, 1983). Five male and five female rats per group were killed at weeks 26-27, 52-53, and 76-77. The remainder were killed at week 108 after a 32-week recovery period. The compound did not affect mortality, clinical condition, body weight, hematologic parameters, or body weight gain at these doses. 1,4-Dichlorobenzene at 500 ppm did increase the liver weight to body weight ratio of male rats slightly at week 76 of exposure (13%), indicating some biologic effects. However, the liver size of animals killed at 108 weeks (after a 32-week recovery period) was no greater than that of control rats, suggesting that the effect had disappeared. The liver weights of female rats were increased over those of controls at 75 and 500 ppm at 26 weeks but not at 76-77 weeks, although the liver weights in the high dose animals were greater than those in controls at 109-112 weeks. Kidney weights were increased in the high dose male rats at 26-27 and 76-77 weeks, but at 109-112 weeks (after the 32-week recovery period), they were similar to those of controls. Excretion of urinary coproporphyrin was purported to be higher at 500 ppm; however, there was so much variation in the mean values for this parameter in different groups of rats that this suggestion does not appear to be valid. 1,4-Dichlorobenzene did not affect the incidence of tumors in rats given this regimen (exposed at 75 or 500 ppm by inhalation for 76 weeks, given a 32-week recovery period, and then killed at 108 weeks). No histologic alterations were noted, however.

In a second study (Riley et al., 1980b, also quoted by Loeser and Litchfield, 1983), groups of 75 male and 75 female SPF Swiss mice (Alderley Park strain) were exposed to 1,4-dichlorobenzene at 75 or 500 ppm by inhalation for 57 weeks. Because of fighting among the males and the probable occurrence during the study of a respiratory infection in both sexes due to a suspected Sendai virus, the male study was terminated at week 61, when mortality was approaching 80%. Exposure of the females ceased at week 57, and the animals were killed at weeks 75-76. Histologic examination of all groups of female mice indicated a high incidence of respiratory disease, but there was no evidence of any compound-related effects. The authors concluded that, within the limitations of the experiments, the administration of 1,4-dichlorobenzene to female mice at levels up to 500 ppm for 57 weeks followed by a recovery period of 19 weeks did not produce any significant nonneoplastic lesions or increase the number or type of neoplasms.

In these inhalation studies, the rats and mice were exposed for fewer than 104 weeks, the usual duration of dosing for carcinogenicity studies in these species (IARC, 1982; NTP, 1984). Moreover, the absence of histologic

alterations in both rats and mice at terminal kill suggests that recovery may have occurred. Also, the doses selected may have been lower than would be chosen according to current practice. There was no evidence of a biologic effect in mice. Riley et al. (1980a) stated that the doses for the rat study were based on a possible effect level based on findings from a study published by Hollingsworth et al. (1956) which was performed in an unspecified strain of rats. However, fewer biologic effects were observed at the 500-ppm level than were anticipated based on the Hollingsworth study. It is doubtful that the inhalation studies reported by Riley et al. (1980a,b) achieved tissue levels comparable to those achieved in the present NTP studies. This inference is based on data reported by Hawkins et al. (1980) which indicated that roughly comparable tissue levels were achieved when female rats were given 1,4-dichlorobenzene orally at doses of 250 mg/kg or by inhalation at 1,000 ppm. In the present NTP 2-year gavage studies, doses of 150 and 300 mg/kg were given to male rats and 300 and 600 mg/kg to females.

Case Reports and Epidemiologic Studies

Girard et al. (1969) reported the occurrence of leukemia in five humans who had been exposed to 1,2- or 1,4-dichlorobenzene as a solvent for other chemicals or in chlorinated benzene mixtures. These included two incidents of chronic lymphatic leukemia, two of myeloblastic leukemia, and one of myeloproliferative syndrome. One of the individuals with chronic lymphatic leukemia had been exposed for several years to a glue containing 2% 1,2-dichlorobenzene, and the other had been exposed to a solvent containing 1,2-, 1,3-, and 1,4-dichlorobenzenes (80%, 2%, and 15%, respectively). One of the persons with myeloblastic leukemia had used this same solvent, and the other had been exposed to a product containing 37% 1,2-dichlorobenzene. The person with myeloproliferative syndrome had been exposed to many chemicals, including 1,2-dichlorobenzene. The authors were unable to conclude that the chlorinated benzenes were the causative agents for these blood disorders but suggested that workers exposed to these solvents should be monitored carefully. The International Agency for Research on Cancer considered these data to be inadequate to evaluate the carcinogenicity of dichlorobenzenes in humans (IARC, 1982).

An increase in chromosomal aberrations was observed in peripheral blood samples from 8 male and 18 female workers accidentally exposed 8 hours per day for 4 days to 1,2-dichlorobenzene vapors; exposure produced symptoms in 10 individuals (headache, malaise, dizziness, and nausea) (Zapata-Gayon et al., 1982). The chief chromosomal alterations were single and double breaks. Six months later, a reduction in the aberrations was observed. No estimates of the levels of exposure or tissue residues were given in this study.

Mutagenicity

Lawlor et al. (1979) examined the genotoxic potential of 1,4-dichlorobenzene with repair-deficient and repair-proficient strains of *Escherichia coli* and Salmonella. 1,4-Dichlorobenzene decreased the survival index for *E. coli* only at the highest dose tested (200 µg/ml). Shimizu et al. (1983) found that 1,4-dichlorobenzene was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 with or without metabolic activation at the highest doses that could be tested without toxicity (6.6 mg/plate). 1,4-Dichlorobenzene was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without activation by Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 at concentrations up to 100 µg/plate when tested according to a preincubation protocol (Haworth et al., 1983; Appendix E, Table E1). 1,4-Dichlorobenzene was reported to be weakly mutagenic to the $meth_3$ locus in *Aspergillus nidulans* (Prasad, 1970); however, the IARC working group suggested that these findings need to be confirmed (IARC, 1982). 1,4-Dichlorobenzene did not increase the frequency of forward mutations in L5178Y/TK$^{+/-}$ mouse lymphoma cells in the absence of metabolic activation (Table E2). In the presence of S9 from Aroclor 1254-induced male F344 rat liver, the results of this test were equivocal in that a first trial gave negative results for mutagenicity, a clearly positive response occurred at the highest dose administered in a second trial, and in a third trial the response at a similar dose was marginal

(Table E3). 1,4-Dichlorobenzene did not induce unscheduled DNA synthesis in human lymphocytes in vitro (Perocco et al., 1983).

Several studies have demonstrated that 1,4-dichlorobenzene produces chromosomal aberrations in root tips (Sharma and Bhattacharyya, 1956; Srivastava, 1966; Gupta, 1972). However, 1,4-dichlorobenzene did not induce chromosomal aberrations or sister-chromatid exchanges in Chinese hamster ovary cells either with or without metabolic activation by Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Tables E4 and E5). Further, in a review of results from an unpublished in vivo mammalian cytogenetics test, Loeser and Litchfield (1983) reported that 1,4-dichlorobenzene produced no increase in the number of chromosomal abnormalities in rat bone marrow cells 22 hours after inhalation exposure to three rats per group under one of the following conditions: 2 hours at 299 or 682 ppm; 5 hours per day for 5 days at 75 or 500 ppm; or 5 hours per day, 5 days per week for 3 months at 75 or 500 ppm. These findings are supported by the negative results in studies conducted by NTP on micronuclei in circulating erythrocytes from mice exposed orally to 1,4-dichlorobenzene for 13 weeks at doses of 600-1,800 mg/kg (Table E6). Loeser and Litchfield (1983) also reviewed previously unpublished data on a dominant lethal assay in which 16 male mice were exposed by inhalation at concentrations of 75, 225, or 450 ppm 1,4-dichlorobenzene 6 hours per day for 5 days. The mice were mated with virgin females each week for 8 weeks. Fertility was not affected. No significant increase in postimplantation early fetal deaths was observed at any time. There was no evidence of preimplantational ovum loss as indicated by the total number of implantations during weeks 1-7, but a decrease in total implantations at 75 and 450 ppm at week 8 was observed. The significance of this decrease was weakened by the absence of an increase in the number of early deaths.

NTP Carcinogenicity Studies of Other Lower Chlorinated Benzenes

Another chlorinated benzene derivative, monochlorobenzene, was studied for toxic and carcinogenic potential by gavage administration to male and female F344/N rats and B6C3F$_1$ mice at doses up to 750 mg/kg body weight per day for 13 weeks and at doses up to 120 mg/kg per day (high dose of 60 mg/kg per day for male mice) for 103 weeks (NTP, 1985a). In the 13-week studies, doses of 250-750 mg/kg per day caused death, hepatocellular necrosis, renal tubular injury, thymic necrosis, or lymphoid or myeloid depletion of the bone marrow, spleen, or thymus in both rats and mice. The dose of 120 mg/kg per day in the 103-week study caused an increased incidence of neoplastic nodules of the liver in male rats. Increased tumor incidences associated with long-term monochlorobenzene administration were not observed in female rats or in male and female mice. No other toxic lesions attributed to monochlorobenzene were detected in the 103-week studies.

1,2-Dichlorobenzene was administered by gavage to male and female F344/N rats and B6C3F$_1$ mice at doses up to 500 mg/kg 5 days per week for 13 weeks and at doses of 60 and 120 mg/kg 5 days per week for 103 weeks (NTP, 1985b). In the 13-week studies, 500 mg/kg of 1,2-dichlorobenzene decreased survival in male and female mice and in female rats and produced centrilobular necrosis, hepatocellular degeneration, and depletion of lymphocytes in the thymus and spleen of both sexes of mice and rats. This dose also produced renal tubular degeneration in male rats and multifocal mineralization of the myocardial fibers of the heart and skeletal muscle in male and female mice. At 250 mg/kg, 1,2-dichlorobenzene produced necrosis of individual hepatocytes in rats and mice of each sex. Minimal hepatocellular necrosis was observed in a few rats at a dose of 125 mg/kg. The only hematologic changes seen at any dose were slight decreases in hemoglobin and hematocrit in male and female rats at 500 mg/kg and a slight decrease in the red blood cell count in male rats at 500 mg/kg.

1,2-Dichlorobenzene caused a slight porphyrinuria (a threefold to fivefold increase in urinary uroporphyrins and coproporphyrins) in male and female rats at 500 mg/kg. However, there was no increase in hepatic porphyrins at any dose in rats or mice, indicating that 1,2-dichlorobenzene was not porphyrogenic in these species. Increases in liver weight to body weight ratios

were seen in male and female rats at 125-500 mg/kg and in mice at 500 mg/kg. There was a dose-related increase in serum cholesterol in male rats at 30-500 mg/kg and in females at 125-500 mg/kg. Total serum proteins were increased at doses of 250-500 mg/kg (male) and 30-500 mg/kg (female). Polyuria was seen in male rats at 500 mg/kg. (Serum analyses were not performed for mice.)

In the 2-year carcinogenicity study, there was an increase in the incidence of pheochromocytomas of the adrenal gland in the low dose male rats (60 mg/kg) relative to vehicle controls; however, there was no increase in the high dose group (vehicle control, 9/50; 60 mg/kg, 16/50; 120 mg/kg, 6/49) (NTP, 1985b). Therefore, the increased incidence of pheochromocytomas in the low dose male rats was not considered to be related to the administration of 1,2-dichlorobenzene. There was no increase in other neoplastic lesions in rats or mice in these studies. There was a decrease in survival of high dose male rats, but aspiration of 1,2-dichlorobenzene in corn oil in the lungs of 12 high dose male rats may have contributed to the early deaths. An increased incidence of tubular regeneration in the kidney of high dose male mice was observed in the 2-year study. There was no evidence of carcinogenicity of 1,2-dichlorobenzene for F344/N rats or $B6C3F_1$ mice under the conditions of the 2-year studies.

Study Rationale

1,4-Dichlorobenzene was studied for toxicity and carcinogenicity because of its extensive production and use and the absence of previous studies to determine its carcinogenic potential. Although the predominant route of human exposure is inhalation, the oral route (gavage) was used because of ease of administration and because humans are exposed via multiple routes including air and drinking water. Moreover, recent studies have shown that the metabolism and distribution of 1,4-dichlorobenzene are similar after gavage administration, inhalation exposure, and subcutaneous injection (Hawkins et al., 1980). The 13-week studies were expanded to include hematologic evaluation and clinical chemistry studies because a few reports suggested that human exposure to the dichlorobenzenes might be associated with hematologic disorders, including leukemia (Girard et al., 1969). Clinical chemistry and urinary porphyrin values were determined in the 13-week studies to assess the effects of this chemical on the liver and kidney.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 1,4-DICHLOROBENZENE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FIRST FOURTEEN-DAY STUDIES

SECOND FOURTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

PROCUREMENT AND CHARACTERIZATION OF 1,4-DICHLOROBENZENE

Technical-grade 1,4-dichlorobenzene was obtained in one lot from Dover Chemical Co., a subsidiary of ICC Solvent Chemical Co. (New York, New York). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix F).

The identity of 1,4-dichlorobenzene was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analysis, Karl Fischer water analysis, and gas chromatography. This lot was greater than 99% pure. Results of elemental analysis were in agreement with theoretical values. No impurities were detected by gas chromatography. (Peaks corresponding to 1,2- and 1,3-dichlorobenzene at the limit of detection, 0.05%, w/w, were not present.) Periodic characterization of the bulk chemical by infrared spectroscopy and gas chromatography confirmed the identity of the chemical and indicated that no detectable deterioration occurred over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

1,4-Dichlorobenzene in corn oil at a concentration of 8% was stable for at least 7 days at room temperature (Appendix G). Formulations of 1,4-dichlorobenzene in corn oil were prepared (Table 1), and samples were periodically selected at random to estimate the accuracy with which the formulations were prepared over the course of the studies. Dose mixtures were analyzed at approximately 8-week intervals during the 2-year studies (Appendixes H and I). All of the samples analyzed were within ± 10% of the target concentrations (Table 2; Table I1).

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

First Fourteen-Day Studies	Second Fourteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
Preparation				
Weighed portion of 1,4-dichlorobenzene and corn oil mechanically stirred in volumetric flask for 1 h; lower doses prepared by serial dilution.	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies
Maximum Storage Time				
14 d	14 d	14 d	14 d	14 d
Storage Conditions				
23° C	23° C	23° C	23° C	23° C

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

	Target Concentration (mg/ml)		
	30	60	120
Mean (mg/ml)	30.7	59.7	121.1
Standard deviation	1.05	2.32	5.44
Coefficient of variation (percent)	3.4	3.9	4.5
Range (mg/ml)	28.4-32.4	56.0-62.4	110.4-127.2
Number of samples	12	12	12

FIRST FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 14 days (rats) or 22 days (mice) before the studies began. 1,4-Dichlorobenzene was administered by gavage in corn oil to groups of five male and five female rats at doses of 60, 125, 250, 500, or 1,000 mg/kg for 14 consecutive days. 1,4-Dichlorobenzene was administered to groups of five male and five female mice at doses of 250, 500, 1,000, 2,000, or 4,000 mg/kg. Controls were untreated.

Animals were housed five per cage. Feed and water were available ad libitum. Details of animal maintenance are presented in Table 3. The rats and mice were observed twice per day. A necropsy was performed on all animals.

SECOND FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 14 days before the studies began.

Groups of five male and five female rats were administered 500, 1,000, 2,000, 4,000, or 8,000 mg/kg 1,4-dichlorobenzene in corn oil by gavage for 14 consecutive days. Groups of five male and five female mice were administered 60, 125, 250, 500, or 1,000 mg/kg. Controls were untreated.

Animals were housed five per cage. Feed and water were available ad libitum. Details of animal maintenance are presented in Table 3. The rats and mice were observed twice per day. A necropsy was performed on all animals.

FIRST THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 1,4-dichlorobenzene and to determine the doses to be used in the 2-year studies.

Four- to five-week-old male and female F344/N rats and 5-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries, observed for 17 days (rats) or 14 days (mice), and assigned to cages according to a table of random numbers. The cages were then assigned to groups according to another table of random numbers.

Groups of 10 rats of each sex were administered 0, 300, 600, 900, 1,200, or 1,500 mg/kg 1,4-dichlorobenzene in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 600, 900, 1,000, 1,500, or 1,800 mg/kg.

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 3.

Animals were checked twice per day; moribund animals were killed. Individual animal weights were recorded weekly. One week before the rats and mice were killed, the animals were placed in metabolism cages and urine was collected for 24 hours. The following analyses were performed: pH, protein, glucose, ketones, bilirubin, occult blood, specific gravity, creatine, uroporphyrins, and coproporphyrins. One day before the animals were killed, blood was withdrawn from the

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

First Fourteen-Day Studies	Second Fourteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females of each species	Same as first 14-d studies	10 males and 10 females of each species	Same as first 13-wk studies	50 males and 50 females of each species
Doses				
Rats--60, 125, 250, 500, or 1,000 mg/kg 1,4-dichlorobenzene in corn oil by gavage; mice--250, 500, 1,000, 2,000, or 4,000 mg/kg 1,4-dichlorobenzene in corn oil by gavage; dose vol--5 ml/kg; rat controls untreated; mouse controls untreated after d 1	Rats--500, 1,000, 2,000, 4,000, or 8,000 mg/kg 1,4-dichlorobenzene in corn oil by gavage; dose vol--20 ml/kg during wk 1, 5 ml/kg during wk 2; controls untreated; mice--60, 125, 250, 500, or 1,000 mg/kg in corn oil by gavage; dose vol--5 ml/kg; controls untreated	Rats--0, 300, 600, 900, 1,200, or 1,500 mg/kg 1,4-dichlorobenzene in corn oil by gavage; mice--0, 600, 900, 1,000, 1,500, or 1,800 mg/kg 1,4-dichlorobenzene in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 37.5, 75, 150, 300, or 600 mg/kg 1,4-dichlorobenzene in corn oil by gavage; mice--0, 84.4, 168.8, 337.5, 675, or 900 mg/kg 1,4-dichlorobenzene in corn oil by gavage; dose vol--5 ml/kg	Male rats--0, 150, or 300 mg/kg 1,4-dichlorobenzene in corn oil by gavage; female rats and mice--0, 300, or 600 mg/kg 1,4-dichlorobenzene in corn oil by gavage; dose vol--5 ml/kg
Date of First Dose				
Rats--1/12/78; mice--1/5/78	Rats--4/13/78; mice--4/12/78	Rats--7/21/78; mice--7/19/78	7/2/79	Rats--5/12/80; mice--5/19/80
Date of Last Dose				
Rats--1/25/78; mice--1/18/78	Rats--4/26/78; mice--4/25/78	Rats--10/19/78; mice--10/17/78	9/28/79	Rats--4/30/82; mice--5/7/82
Duration of Dosing				
14 consecutive d	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation				
Observed 2 × d	Same as first 14-d studies	Observed 2 × d; weighed 1 × wk	Same as first 13-wk studies	Observed 2 × d; weighed initially, 1 × wk for 13 wk, then monthly
Necropsy and Histologic Examination				
Necropsy performed on all animals; selected animals received histologic exam	Same as first 14-d studies except no histologic exams on rats	Necropsy performed on all animals; histologic exam on all vehicle controls, 3 highest dose groups of rats, and 2 highest dose groups of mice; kidneys and lungs examined from 600 mg/kg rats and 300 mg/kg male rats; liver and gallbladder of 600, 900, and 1,000 mg/kg male mice. Tissues examined: gross lesions, skin lesions (if present), mammary gland, salivary gland, quadriceps muscle, sciatic nerve, sternum with bone marrow, thymus, larynx, trachea, lungs, heart, thyroid	Necropsy performed on all animals; tissues examined are the same as in first 13-wk studies.	Necropsy and histologic exam performed on all animals; the following tissues were examined: gross lesions and tissue masses, regional lymph nodes, mandibular or mesenteric lymph nodes, salivary gland, femur including bone marrow, thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, heart, esophagus, stomach, brain, thymus, spleen, pancreas, skin, trachea, lungs and mainstem bronchi, kidneys, adrenal glands, urinary bladder, pituitary

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (Continued)

First Fourteen-Day Studies	Second Fourteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Necropsy and Histologic Examination (Continued)				
		gland, parathyroids, esophagus, stomach, duodenum, right pinna, aorta, ear canal, right eye, tissue masses and regional lymph nodes, ileum, colon, cecum, mesenteric and thoracic lymph nodes, liver, pancreas, spleen, right kidney, adrenal glands, urinary bladder, testes or ovary/uterus, nasal turbinates, brain, pituitary gland, and spinal cord/lumbar		gland, eyes (if grossly abnormal), and mammary gland
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	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source				
Harlan Industries, Inc. (Cumberland, IN)	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory				
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification				
Toe clip	Toe clip	Toe clip	Toe clip	Toe clip
Time Held Before Study				
Rats--14 d; mice--22 d	14 d	Rats--17 d; mice--14 d	17 d	Rats--17 d; mice--14 d
Age When Placed on Study				
Rats--6 wk; mice--8 wk	Same as first 14 d studies	Rats--6 wk; mice--7 wk	7 wk	Rats--7 wk; mice--8 wk
Age When Killed				
Rats--9 wk; mice--11 wk	Rats--8 wk; mice--10 wk	Rats--20 wk; mice--21 wk	20 wk	Rats--111 wk; mice--112 wk
Necropsy Dates				
Rats--1/31/78; mice--1/23/78	Rats--4/28/78; mice--4/27/78	Rats--10/23/78-10/24/78; mice--10/19/78-10/20/78	10/1/79-10/2/79	Rats--5/10/82-5/13/82; mice--5/18/82-5/20/82
Method of Animal Distribution				
Assigned to cages by table of random numbers, then to groups by another table	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (Continued)

First Fourteen-Day Studies	Second Fourteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Feed				
Purina Lab Chow (Ralston Purina, St. Louis, MO); available ad libitum	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum
Bedding				
Absorb-Dri (Lab Products, Garfield, NJ)	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies
Water				
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies
Cages				
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies
Cage Filters				
Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies
Animals per Cage				
5	5	5	5	5
Other Chemicals on Study in the Same Room				
None	None	None	None	None
Animal Room Environment				
Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies	Same as first 14-d studies

orbital venous plexus and analyzed for hemoglobin, hematocrit, total and differential white blood cell count, red blood cell count, mean corpuscular volume, platelet count, and reticulocyte count. On the day the animals were killed, they were anesthesized with sodium pentobarbital and blood samples were withdrawn by cardiac puncture. The following analyses were performed: alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT), *gamma*-glutamyltranspeptidase, bilirubin, cholesterol, triglycerides, blood urea nitrogen, glucose, total protein, and globulin fractions. $Alpha_1$ and $alpha_2$ globulin fractions were combined because of the low concentrations present. The methods of analysis are described in Appendix J.

The following organs were weighed: lung, heart, liver, spleen, thymus, right kidney, brain, right testicle or right ovary, and uterus. Liver samples were analyzed by the method of Abritti and DeMatteis (1971-1972).

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 3.

Statistical analyses were performed on the organ weight, clinical chemistry, and hematology data to assess the significance of differences among dosed and vehicle control group means. These analyses involved the multiple comparison procedures of Dunnett (1955) or Williams (1971, 1972). Williams' test is designed to detect compound-related differences when the response consistently increases (or decreases) as the dose increases. Although the test employs a smoothing algorithm to adjust for dose-response inversions, Dunnett's test is more appropriate if the departure from monotonicity is severe. To assess this departure, Jonckheere's (1954) test for a dose-related trend was applied. If the Jonckheere P value was greater than 0.15, Dunnett's test was used in place of Williams' test.

SECOND THIRTEEN-WEEK STUDIES

The 13-week studies were rerun because a no-effect dose was not achieved in the first 13-week studies.

Four-week-old male and female F344/N rats and 5-week-old male and female $B6C3F_1$ mice were obtained from Harlan Industries, observed for 17 days, and assigned to cages according to a table of random numbers. The cages were then assigned to dosed and vehicle control groups according to another table of random numbers.

Groups of 10 rats of each sex were administered 0, 37.5, 75, 150, 300, or 600 mg/kg 1,4-dichlorobenzene in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 84.4, 168.8, 337.5, 675, or 900 mg/kg.

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further experimental details are summarized in Table 3. Animals were checked twice per day; moribund animals were killed. Individual animal weights were recorded weekly.

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 3.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 150, or 300 mg/kg 1,4-dichlorobenzene, 5 days per week for 103 weeks. Groups of 50 female rats and 50 male and female mice were administered 0, 300, or 600 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation 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. Rats were shipped to the study laboratory at 5 weeks of age and mice at 6 weeks. The rats were quarantined at the study facility for 17 days and the mice for 14 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 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 K).

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/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice 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/6 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. Further details of animal maintenance are given in Table 3.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 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 found 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. Tissues examined microscopically are listed in Table 3.

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 lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic 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 dead of other than natural causes or were found to be missing; 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. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration 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 analysis of tumor incidence, and reported P values are one-sided.

Life Table Analyses--The first method of analysis assumed 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 vehicle 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 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.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval.

The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods).

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, 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 primary 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.

III. RESULTS

RATS

FIRST FOURTEEN-DAY STUDIES

SECOND FOURTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FIRST FOURTEEN-DAY STUDIES

SECOND FOURTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FIRST FOURTEEN-DAY STUDIES

One male rat in the 125 mg/kg group died before the end of the studies (Table 4). This animal had a punctured esophagus, indicating probable gavage error. The final mean body weights of dosed male rats were 7%-12% lower than that of the controls; however, there was no clear dose-related trend. The final mean body weights of the female rats were not affected in a dose-related manner. No compound-related effects were observed at necropsy or after microscopic examination in either sex. Thus, additional 14-day studies were performed at higher doses.

SECOND FOURTEEN-DAY STUDIES

All rats receiving 1,4-dichlorobenzene at 2,000, 4,000, or 8,000 mg/kg died before the end of the studies (Table 5). Four of five females died in the 1,000 mg/kg group; the death of one male rat at this dose was due to gavage error. The final mean body weight of male rats receiving 500 or 1,000 mg/kg 1,4-dichlorobenzene was 9% or 14% lower than that of the controls, and weight gain was also lower than that of the controls (Table 5). The final body weight of the single surviving female rat receiving 1,000 mg/kg was 17% lower than that of the controls, but the 500 mg/kg dose did not affect final body weight or weight gain of female rats. The reason for the discrepancy in survival of female rats at 1,000 mg/kg is not readily apparent. However, a high dose of 1,500 mg/kg was selected for the 13-week studies, since there were deaths in females but not in males at 1,000 mg/kg in these studies.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIRST FOURTEEN-DAY GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
(d) 0	5/5	125	183	+58	--
60	5/5	124	170	+46	92.9
125	(e) 4/5	120	166	+46	90.7
250	5/5	126	174	+48	95.1
500	5/5	123	168	+45	91.8
1,000	5/5	118	161	+43	88.0
FEMALE					
(d) 0	5/5	95	122	+27	--
60	5/5	99	121	+22	99.2
125	5/5	99	122	+23	100.0
250	5/5	95	117	+22	95.9
500	5/5	92	119	+27	97.5
1,000	5/5	98	130	+32	106.6

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean group body weight change
(d) Controls were untreated.
(e) Day of death: 8

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SECOND FOURTEEN-DAY GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	112	192	+80	--
500	5/5	118	175	+57	91.1
1,000	(e) 4/5	110	166	+56	86.5
2,000	(f) 0/5	115	(g)	(g)	(g)
4,000	(h) 0/5	116	(g)	(g)	(g)
8,000	(i) 0/5	108	(g)	(g)	(g)
FEMALE					
(d) 0	5/5	100	132	+32	--
500	(j) 4/5	99	134	+35	101.5
1,000	(k) 1/5	92	110	+18	83.3
2,000	(l) 0/5	94	(g)	(g)	(g)
4,000	(i) 0/5	97	(g)	(g)	(g)
8,000	(i) 0/5	99	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean group body weight change
(d) Controls were untreated.
(e) Death due to gavage technique
(f) Day of death: 2, 3, 3, 3, 3
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 1, 2, 2, 2, 2
(i) Day of death: all 2
(j) Day of death: 13
(k) Day of death: 1, 4, 5, 5
(l) Day of death: 2, 2, 2, 2, 3

FIRST THIRTEEN-WEEK STUDIES

The doses selected for the first 13-week studies are given in Table 6. Presumably the 900, 1,200, and 1,500 mg/kg doses were spaced closely because of differences in lethality of the 1,000 mg/kg dose in the first and second 14-day studies. Eight of 10 male and 9/10 female rats receiving 1,500 mg/kg 1,4-dichlorobenzene, 5/10 males and 1/10 females receiving 1,200 mg/kg, and 1/10 male and 2/10 females receiving 900 mg/kg died before the end of the studies (Table 6). 1,4-Dichlorobenzene significantly ($P<0.01$) depressed body weight gain of male rats in the 600, 900, 1,200, and 1,500 mg/kg groups. In female rats, body weight gain was significantly decreased at 1,200 mg/kg. No comparison was made at 1,500 mg/kg, since only one female rat survived.

Tremors, poor motor response, and ocular discharge were noted before death in the 1,200 mg/kg group of males and in the 1,500 mg/kg groups of males and females. Degeneration and necrosis of hepatocytes, hypoplasia of the bone marrow, lymphoid depletion of the spleen and thymus, epithelial necrosis and villar bridging of the small intestinal mucosa, and epithelial necrosis of the nasal turbinates were observed in the rats receiving 1,200 or 1,500 mg/kg but not in those receiving 900 mg/kg or less. Most of the dosed male rats that survived 45 days or more had a renal lesion characterized by multifocal degeneration or necrosis of the renal cortical tubular epithelial cells with amorphous eosinophilic material in the lumens of the affected tubules. There was an increase in the number and size of eosinophilic droplets in the cytoplasm of epithelial cells of the proximal

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	127 ± 2	314 ± 6	+187 ± 5	--
300	10/10	118 ± 3	281 ± 9	(e) +163 ± 8	89
600	10/10	121 ± 1	263 ± 6	(f) +142 ± 5	84
900	(g) 9/10	121 ± 2	259 ± 7	(f) +137 ± 6	82
1,200	(h) 5/10	122 ± 4	238 ± 13	(f) +114 ± 9	76
1,500	(i) 2/10	118 ± 3	213 ± 23	(f) +91 ± 22	68
FEMALE					
0	10/10	104 ± 2	174 ± 5	+70 ± 4	--
300	10/10	106 ± 3	177 ± 5	+71 ± 5	102
600	10/10	102 ± 2	168 ± 3	+66 ± 3	97
900	(j) 8/10	103 ± 2	164 ± 3	+60 ± 4	94
1,200	(g) 9/10	103 ± 3	155 ± 6	(f) +51 ± 4	89
1,500	(k) 1/10	103 ± 2	140	(l) +29	80

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean group body weight change of the survivors ± standard error of the mean
(d) Week of death: 10
(e) Significant decrease, $P<0.05$ versus the vehicle controls by Williams' test
(f) Significant decrease, $P<0.01$ versus the vehicle controls by Williams' test
(g) Week of death: 1
(h) Week of death: 4, 7, 8, 13, 13
(i) Week of death: 1, 1, 1, 1, 1, 1, 6, 10
(j) Week of death: 1, 5
(k) Week of death: 1, 2, 3, 4, 5, 5, 7, 9, 13
(l) Data not analyzed because only one animal survived

convoluted tubules. Reexamination by NTP pathologists of kidney slides stained with Mallory's Heidenhain stain confirmed the increase in the number and size of droplets in these cells. Some thickening of tubular basement membranes was present. Renal tubular cell degeneration was observed in 9/10 or 10/10 male rats receiving 300-1,200 mg/kg and in 3/10 males receiving 1,500 mg/kg. Kidney damage was not noted in dosed female rats. Lymphocytic perivasculitis in the lung was observed at increased incidence in male rats that received 600 or 900 mg/kg.

1,4-Dichlorobenzene produced significant increases in liver weight to brain weight ratios in male and female rats receiving doses of 900 mg/kg or more (Appendix M, Table M1). Organ weight to brain weight ratios are reported in the present studies rather than organ weight or organ weight to body weight ratios because 1,4-dichlorobenzene produced marked decreases in final body weights of all dosed male rats and female rats dosed with 1,200 mg/kg or more. Kidney weight to brain weight ratios were increased significantly in male rats at doses of 600-1,200 mg/kg.

1,4-Dichlorobenzene produced a slight decrease in the hematocrit level in male rats in all dosed groups and a larger decrease (from 50.1% to 42.5%) in the two surviving male rats at 1,500 mg/kg (Table M3). This effect was accompanied by a modest but statistically significant decrease in the red blood cell count and the hemoglobin concentration in male rats at all doses. There was a significant increase relative to the vehicle controls in the percent of reticulocytes only at

300 and 900 mg/kg. None of these hematologic changes was consistently seen in female rats. However, mean corpuscular volume was significantly decreased in male rats at doses of 900 mg/kg or more and in female rats at 600 mg/kg or more. Hematologic and clinical chemistry parameters were not analyzed in female rats at 1,500 mg/kg, and clinical chemistry parameters were not analyzed in male rats at this dose because of poor survival.

In male rats, serum triglyceride levels were reduced by doses of 300 mg/kg or more, whereas the concentration of serum cholesterol was significantly increased over that in vehicle controls at 600 mg/kg or more (Table M3). These two changes may reflect effects of the compound on hepatic function. Total serum protein levels were significantly reduced at doses of 300, 600, and 900 mg/kg. Alkaline phosphatase activity was significantly reduced at 300 mg/kg or more. Although the latter two changes are statistically significant, the biologic implications are modest and the causes of such changes could be nonspecific. In female rats, the serum cholesterol level was significantly increased at doses of 900 and 1,200 mg/kg. The total protein level was significantly increased at doses of 900 and 1,200 mg/kg. Alkaline phosphatase activity was significantly increased at 1,200 mg/kg. There were no significant changes in SGPT activity in male or female rats at any dose. Blood urea nitrogen concentration was increased slightly in male rats dosed with 900 or 1,200 mg/kg but not in female rats.

An approximately threefold increase was observed in urinary uroporphyrin excretion and a sixfold increase in urinary coproporphyrin excretion in male rats dosed with 1,200 or 1,500 mg/kg (Table M3). Urinary uroporphyrin excretion was not increased significantly in female rats at 1,200 mg/kg, but coproporphyrin was increased twofold at this dose. Urine from male and female rats in other dose groups was not analyzed. However, liver porphyrin levels were not increased significantly in either sex at any dose (300-1,500 mg/kg).

Since administration of 1,4-dichlorobenzene to male rats produced histologic changes in the kidney which were judged to be potentially life threatening at all doses in this study, the 13-week studies were repeated at lower doses (37.5-600 mg/kg).

SECOND THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 7). Body weight gains of dosed and vehicle control rats were comparable in each sex.

An increase in the incidence and severity of kidney cortical tubular degeneration was observed in male rats receiving 600 mg/kg of 1,4-dichlorobenzene (vehicle control, 7/10, mild; 150 mg/kg, 5/10, mild-moderate; 300 mg/kg, 3/10, moderate; 600 mg/kg, 9/10, moderate). No compound-related histopathologic effects were observed in female rats.

Dose Selection Rationale: Based on histopathologic effects observed in male rats, 1,4-dichlorobenzene doses selected for the 2-year studies were 150 and 300 mg/kg for male rats and 300 and 600 mg/kg for female rats. The principal data considered for this dose selection were as follows: body weight changes in male but not in female rats at 300 mg/kg in the first studies and an increase in the incidence of renal tubular change in male rats; weight loss, hepatocellular damage, and deaths of female rats at 1,200 mg/kg but not at 600 mg/kg; no body weight change in the second studies, but renal tubular changes confirmed in male rats at 600 mg/kg with some indication of a slight increase in severity at 300 mg/kg. The doses were to be administered in corn oil by gavage, 5 days per week.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	158 ± 10	327 ± 7	+169 ± 12	--
37.5	10/10	144 ± 9	316 ± 7	+172 ± 9	97
75	9/10	149 ± 9	335 ± 8	+181 ± 14	102
150	9/10	153 ± 9	314 ± 6	+164 ± 11	96
300	10/10	153 ± 9	324 ± 7	+171 ± 7	99
600	8/10	140 ± 10	322 ± 6	(d) +173 ± 14	98
FEMALE					
0	10/10	100 ± 1	187 ± 3	+87 ± 3	--
37.5	9/10	99 ± 1	187 ± 2	+88 ± 2	100
75	10/10	102 ± 2	187 ± 3	+85 ± 3	100
150	9/10	102 ± 1	187 ± 2	+86 ± 3	100
300	8/10	100 ± 2	192 ± 3	+92 ± 4	103
600	8/10	99 ± 2	189 ± 3	+89 ± 3	101

(a) Number surviving/number initially in group; all deaths were due to gavage error.
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean group body weight change of the survivors ± standard error of the mean
(d) The final body weight (205 g) of one animal with hydrocephalus was excluded from calculations.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were generally 5%-8% lower than those of the vehicle controls after week 38 (Table 8 and Figure 1).

Mean body weights of high dose female rats were 5%-7% lower than those of the vehicle controls after week 55.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Weeks on Study	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE	**Vehicle Control**		**150 mg/kg**			**300 mg/kg**		
0	188	50	189	101	50	185	98	50
1	219	50	220	100	50	216	99	50
2	238	50	237	100	50	228	96	50
3	260	50	260	100	50	253	97	50
4	272	50	264	97	50	265	97	49
5	289	50	286	99	50	284	98	49
6	300	50	297	99	50	293	98	49
7	307	50	306	100	50	303	99	49
8	323	50	318	98	50	318	98	49
9	328	50	328	100	50	329	100	49
10	332	50	331	100	50	330	99	49
11	341	50	336	99	50	337	99	49
12	345	50	341	99	50	340	99	49
16	376	50	368	98	50	362	96	49
20	397	50	388	98	50	398	100	49
25	419	49	413	99	50	403	96	49
29	431	49	421	98	50	412	96	49
34	447	49	436	98	50	429	96	49
38	460	49	451	98	48	436	95	49
42	466	49	459	98	46	447	96	49
46	477	48	467	98	45	446	94	48
51	488	47	477	98	44	464	95	48
55	494	47	481	97	44	467	95	48
59	494	47	481	97	42	469	95	48
64	491	47	482	98	41	465	95	44
68	490	45	479	98	41	462	94	44
72	497	44	472	95	40	457	92	42
77	498	43	474	95	40	458	92	39
81	496	43	477	96	39	474	96	36
86	486	43	476	98	37	466	96	32
91	482	37	471	98	35	448	93	30
95	479	35	467	97	35	445	93	28
100	464	33	458	99	34	429	92	25
103	461	33	450	98	31	424	92	21
FEMALE	**Vehicle Control**		**300 mg/kg**			**600 mg/kg**		
0	128	50	128	100	50	128	100	50
1	142	50	146	103	50	146	103	50
2	153	50	154	101	50	155	101	50
3	164	50	164	100	50	163	99	50
4	168	50	169	101	50	166	99	50
5	178	50	177	99	50	176	99	50
6	179	50	179	100	50	180	101	50
7	183	50	185	101	50	186	102	50
8	192	50	194	101	50	195	102	50
9	195	50	198	102	50	201	103	50
10	195	50	197	101	50	199	102	50
11	198	50	197	99	50	198	100	50
12	199	50	201	101	50	199	100	49
16	207	50	208	100	50	208	100	49
20	217	50	217	100	50	217	100	49
25	223	50	223	100	50	221	99	47
29	230	50	229	100	50	225	98	47
34	237	50	236	100	50	229	97	47
38	240	49	240	100	50	234	98	47
42	244	49	245	100	50	237	97	47
46	252	49	253	100	50	242	96	47
51	265	49	265	100	50	255	96	47
55	273	49	269	99	50	257	94	47
59	286	49	279	98	50	265	93	45
64	291	49	287	99	50	272	93	44
68	292	48	290	99	49	276	95	44
72	296	48	291	98	48	274	93	42
77	302	48	300	99	47	281	93	41
81	307	47	306	100	47	288	94	41
86	307	46	309	101	46	292	95	39
91	315	43	317	101	43	295	94	37
95	312	43	317	102	42	298	96	35
100	318	40	316	99	40	300	94	33
103	322	35	315	98	39	298	93	29

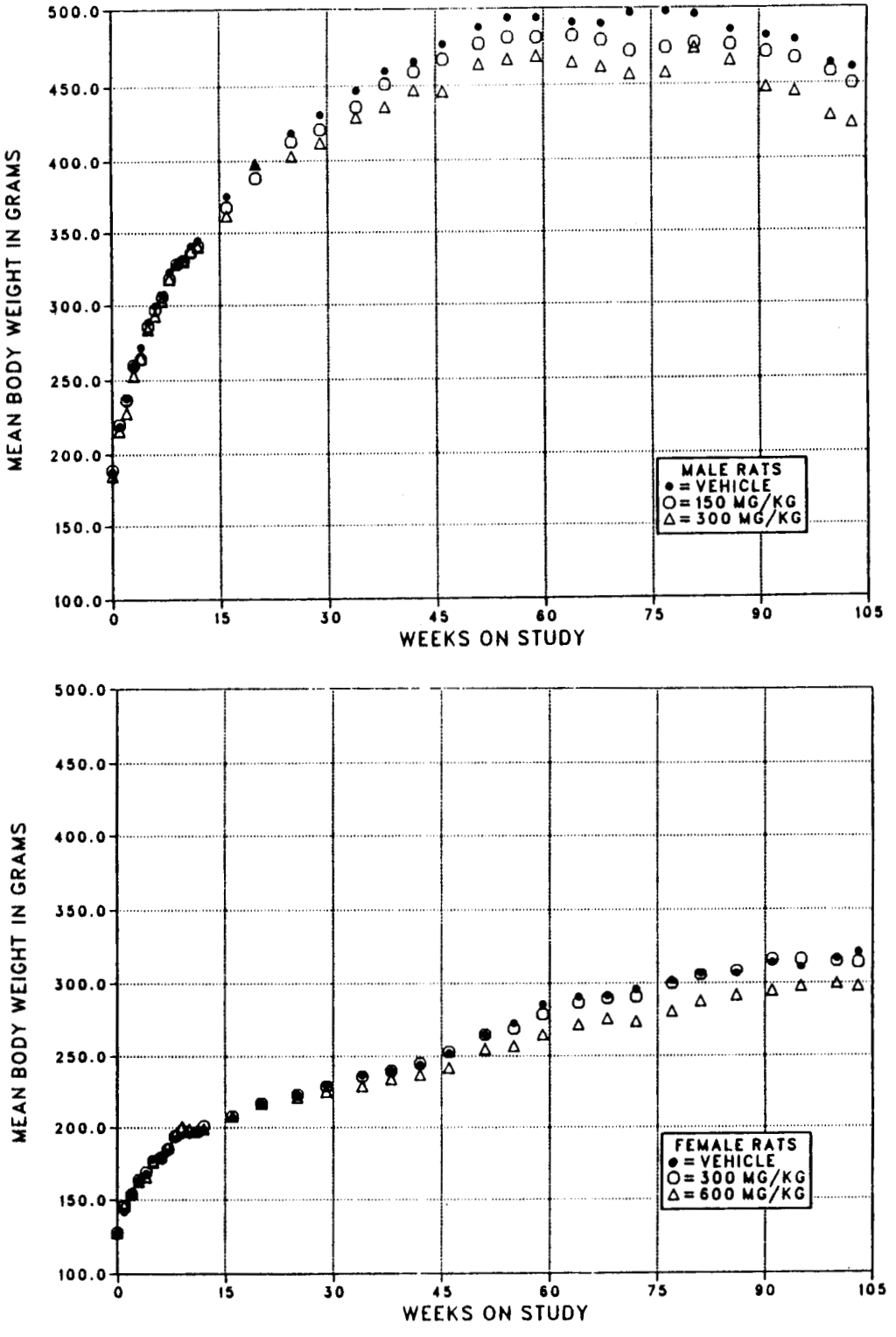

FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED 1,4-DICHLOROBENZENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 1,4-dichlorobenzene at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the high dose male group was significantly lower than that of the vehicle controls after week 97 (Table 9). No significant differences in survival were observed between any female groups.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, hematopoietic system, multiple organs, and parathyroid.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Findings on nonneoplastic lesions are summarized in Table B4.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

	Vehicle Control	Low Dose	High Dose
MALE (a)		**150 mg/kg**	**300 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	14	26
Accidentally killed	7	5	4
Killed at termination	32	31	20
Survival P values (c)	0.003	0.597	0.005
FEMALE (a)		**300 mg/kg**	**600 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	10	18
Accidentally killed	0	1	3
Killed at termination	35	39	29
Survival P values (c)	0.387	0.409	0.439

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

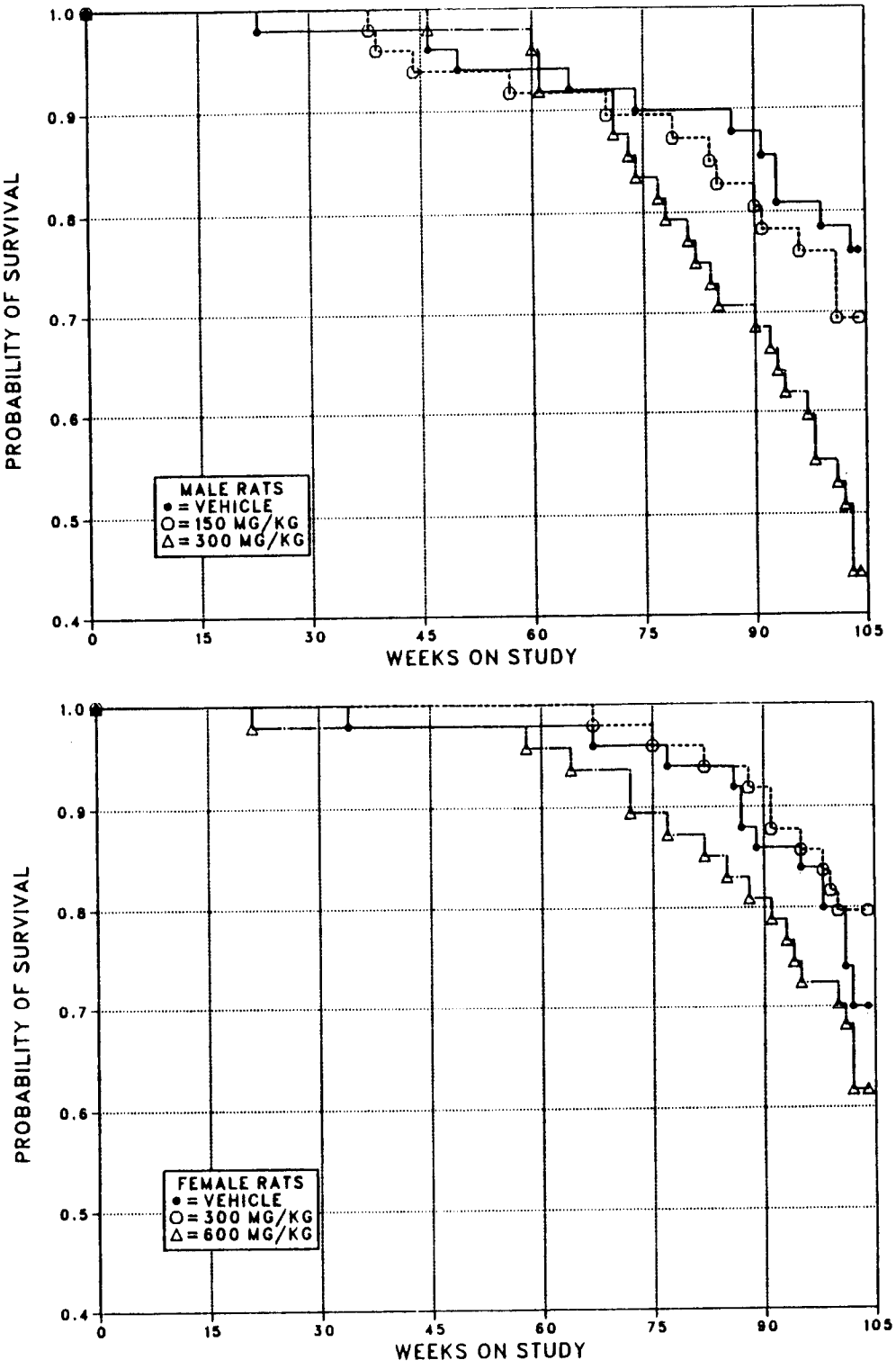

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 1,4-DICHLOROBENZENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: 1,4-Dichlorobenzene increased the incidence of nephropathy in low and high dose female rats (Table 10). The incidences of nephropathy were similar among vehicle control and 1,4-dichlorobenzene-dosed male rats, but the average severity of the lesion was greater in dosed male rats. This lesion was characterized by the occurrence of several interrelated changes, including degeneration and regeneration of tubular epithelium, tubular dilatation with attenuation and atrophy of the epithelium, granular casts in tubules of the outer stripe of the medulla, thickening of basement membranes, and minimal accumulation of interstitial collagen. 1,4-Dichlorobenzene also increased the incidences of mineralization of collecting tubules in the renal medulla of low and high dose groups of male rats, focal hyperplasia of the renal tubular epithelium in high dose male rats, and hyperplasia of the pelvic urothelium overlying the renal papillae of low and high dose groups of male rats compared with the vehicle controls. The intensity of the mineralization was generally minimal in vehicle controls, mild to moderate in low dose males, and moderate to severe in high dose male rats. Focal hyperplasia of the renal tubular epithelium consisted of single or multiple cross-sections of tubules filled or partially filled with stratified epithelial cells. The stratification of these cells and loss of basement membrane dependency differentiates this lesion from the epithelial regeneration occurring in response to the degenerative changes in the kidney. Hyperplasia of the renal pelvic epithelium was minimal to mild in severity and was characterized by thickening and folding of the transitional epithelium to form small nodular structures protruding into the pelvic lumen.

Tubular cell adenocarcinomas and one adenoma occurred in the kidney of dosed male rats (Table 11). Two tumors in the low dose and two tumors in the high dose male rats were grossly visible at necropsy. The incidences of adenocarcinomas and adenomas or adenocarcinomas (combined) in the high dose males were significantly greater than those in the vehicle controls. The renal tumors were observed at multiple kidney sites in two high dose males, and the tumor metastasized to other organs in one high dose male. No renal tumors were observed in any female rats.

TABLE 10. NUMBERS OF RATS WITH KIDNEY LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Site/Lesion	Male			Female		
	Vehicle Control	150 mg/kg	300 mg/kg	Vehicle Control	300 mg/kg	600 mg/kg
Number of rats examined	50	50	50	49	50	49
Kidney						
Nephropathy	42	42	46	21	32	41
Cortex						
Cysts	0	1	7	0	1	1
Medulla						
Mineralization	4	46	47	5	1	10
Tubule						
Focal hyperplasia	0	1	9	0	0	0
Pelvis						
Epithelial hyperplasia	1	30	31	0	0	2
Tubular cell						
Adenoma	0	0	1	0	0	0
Adenocarcinoma	1	3	7	0	0	0

TABLE 11. ANALYSIS OF KIDNEY LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	150 mg/kg	300 mg/kg
Pelvic Epithelial Cell Hyperplasia			
Overall Rates	1/50 (2%)	30/50 (60%)	31/50 (62%)
Tubular Cell Hyperplasia, Focal			
Overall Rates	0/50 (0%)	1/50 (2%)	9/50 (18%)
Tubular Cell Adenoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Tubular Cell Adenocarcinoma			
Overall Rates	1/50 (2%)	3/50 (6%)	7/50 (14%)
Adjusted Rates	3.1%	9.2%	25.7%
Terminal Rates	1/32 (3%)	2/31 (6%)	2/20 (10%)
Week of First Observation	104	101	46
Life Table Tests	P=0.005	P=0.301	P=0.011
Incidental Tumor Tests	P=0.022	P=0.278	P=0.037
Tubular Cell Adenoma or Adenocarcinoma (b)			
Overall Rates	1/50 (2%)	3/50 (6%)	8/50 (16%)
Adjusted Rates	3.1%	9.2%	28.0%
Terminal Rates	1/32 (3%)	2/31 (6%)	2/20 (10%)
Week of First Observation	104	101	46
Life Table Tests	P=0.002	P=0.301	P=0.006
Incidental Tumor Tests	P=0.012	P=0.278	P=0.022

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence at study laboratory (mean): 1/150 (0.7%); historical incidence in NTP studies: 5/1,098 (0.5%)

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a positive trend by the life table test (Table 12). This is the appropriate test, since this tumor is usually lethal. The incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test; however, the incidence in the high dose group was only slightly greater than that of the average historical incidence in corn oil vehicle control male F344/N rats at this laboratory (17%). Mononuclear cell leukemia was not increased in dosed female rats (vehicle control, 15/50; 300 mg/kg, 10/50; 600 mg/kg, 9/50).

Multiple Organs: Mesotheliomas in male rats occurred with a significant positive trend (P=0.041) by the life table test; however, the incidences in the dosed groups were not significantly different from that in the vehicle controls (vehicle control, 1/50; 150 mg/kg, 0/50; 300 mg/kg, 4/50). No mesotheliomas were reported in female rats. The incidences of this tumor in dosed animals are not considered to be related to administration of the chemical.

Parathyroid: Hyperplasia was observed at increased incidences in dosed male rats (vehicle control, 4/42, 10%; 150 mg/kg, 13/42, 31%; 300 mg/kg, 20/38, 53%). Parathyroid hyperplasia was not observed in female rats.

TABLE 12. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	150 mg/kg	300 mg/kg
Overall Rates	5/50 (10%)	7/50 (14%)	11/50 (22%)
Adjusted Rates	12.8%	19.6%	32.1%
Terminal Rates	2/32 (6%)	4/31 (13%)	2/20 (10%)
Week of First Observation	65	57	73
Life Table Tests	P=0.025	P=0.349	P=0.040
Incidental Tumor Tests	P=0.221	P=0.331	P=0.300

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 25/150 (17% ± 3%); historical incidence in NTP studies: 152/1,100 (14% ± 8%)

FIRST FOURTEEN-DAY STUDIES

All male and female mice that received 4,000 mg/kg 1,4-dichlorobenzene were dead by day 4 (Table 13). Two male vehicle controls and one female vehicle control died as a result of gavage error. The final mean body weight of male mice that received 2,000 mg/kg was 15% lower than that of the controls. No compound-related histopathologic effects were noted. Although only some of the deaths appeared to be due to gavage error, a maximum tolerated dose could not be established because of the scattered pattern of deaths in all dosed groups in these 14-day studies. Therefore, the 14-day studies were repeated with lower doses.

SECOND FOURTEEN-DAY STUDIES

No compound-related deaths occurred (Table 14). The one male mouse that died in the 125 mg/kg group had an esophageal rupture. Final mean body weights were not dose related. Therefore, the doses in these studies were too low. Neither of these 14-day studies is considered to be definitive. However, all the mice at 4,000 mg/kg died in the first 14-day studies and no mice died in the second 14-day studies at 1,000 mg/kg. Therefore, the highest dose selected for the 13-week studies was 1,800 mg/kg.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIRST FOURTEEN-DAY GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	(e) 3/5	23.8	28.1	+4.3	--
250	(f) 2/5	24.0	24.4	+0.4	86.7
500	(g) 1/5	22.4	25.7	+3.3	91.4
1,000	(h) 1/5	23.6	26.1	+2.5	92.8
2,000	(i) 1/5	22.4	24.0	+1.6	85.3
4,000	(j) 0/5	24.0	(k)	(k)	(k)
FEMALE					
(d) 0	(e) 4/5	19.4	21.4	+2.0	--
250	(l) 2/5	18.0	20.9	+2.9	97.7
500	(m) 0/5	17.4	(k)	(k)	(k)
1,000	(n) 2/5	18.6	21.4	+2.8	99.8
2,000	(o) 3/5	19.2	22.9	+3.7	107.2
4,000	(p) 0/5	19.0	(k)	(k)	(k)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean group body weight change
(d) Controls untreated after day 1
(e) Deaths due to gavage error
(f) Day of death: 6, 6, 7
(g) Day of death: 3, 5, 5, 8
(h) Day of death: 5, 7, 8, 8
(i) Day of death: 4, 6, 7, 7
(j) Day of death: 2, 2, 2, 2, 4
(k) No data are presented due to the 100% mortality in this group.
(l) Day of death: 5, 5, 6
(m) Day of death: 3, 3, 4, 4, 5
(n) Day of death: 3, 8, 12
(o) Day of death: 5, 8
(p) Day of death: 2, 2, 3, 3, 3

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SECOND FOURTEEN-DAY GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	25.0	27.8	+ 2.8	--
60	5/5	25.2	26.0	+ 0.8	93.5
125	(e) 4/5	25.4	27.0	+ 1.6	97.1
250	5/5	25.0	26.0	+ 1.0	93.5
500	5/5	25.2	27.8	+ 2.6	100.0
1,000	5/5	24.8	27.8	+ 3.0	100.0
FEMALE					
(d) 0	5/5	18.6	21.0	+ 2.4	--
60	5/5	18.6	20.0	+ 1.4	95.2
125	5/5	18.8	19.8	+ 1.0	94.3
250	5/5	19.6	20.4	+ 0.8	97.1
500	5/5	19.8	20.2	+ 0.4	96.2
1,000	5/5	17.6	20.2	+ 2.6	96.2

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean group body weight change of the survivors
(d) Controls were untreated.
(e) Death due to gavage accident

FIRST THIRTEEN-WEEK STUDIES

Seven of 10 male mice and 9/10 female mice that received 1,800 mg/kg died before the end of the studies (Table 15). The incidences of deaths in other groups are tabulated in Table 15. Body weight gain of male and female mice was significantly lower in all dose groups except for female mice that received 1,500 or 1,800 mg/kg. Weight gain of the 1,800 mg/kg female mice was not analyzed because only one animal survived.

The livers of all mice were examined under long-range ultraviolet light at necropsy. No positive red fluorescence indicative of porphyria was observed. Hepatocellular degeneration was observed microscopically at increased incidences in all groups of dosed mice. The incidences were 7/10 and 9/10 for males and females in the 600 mg/kg groups, 10/10 for males and females in the 900, 1,000, and 1,500 mg/kg groups, and 5/10 and 6/10 for males and females in the 1,800 mg/kg groups. The hepatocellular degeneration was centrilobular in distribution and was associated with cytomegaly, variation in nuclear shape, karyomegaly, and granular amphophilic cytoplasm. The severity of this change was dose related. Lymphoid necrosis in the thymus, lymphoid depletion in the spleen, and hematopoietic hypoplasia of the spleen and bone marrow were also noted in animals in the 1,500 and 1,800 mg/kg dose groups which died before the end of the studies.

The liver weight to brain weight ratios were significantly increased relative to vehicle controls in the male and female mice that received 900, 1,000, or 1,500 mg/kg and in male mice that received 1,800 mg/kg (Appendix M, Table M2). Organ weight to brain weight ratios were not analyzed for high dose female mice because of poor survival. Spleen weight to brain weight ratios were significantly reduced relative to vehicle controls in all male dosed groups but not in female dosed groups. The ovary weight to brain weight ratio was significantly increased at 1,500 mg/kg.

The hematocrit value was not significantly altered in either sex (Table M4). The white blood cell count was significantly reduced (34%-50%) in all dosed male groups and in the 1,000 and

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	23.7 ± 0.4	35.9 ± 0 7	+12 1 ± 0 8	--
600	10/10	23 0 ± 0.5	30 9 ± 0 7	(e) +7 9 ± 0 4	86 1
900	10/10	23.1 ± 0 7	32 1 ± 1 1	(e) +9 0 ± 0 8	89 4
1,000	(f) 9/10	22.0 ± 0.7	31 4 ± 1 2	(e) +9 3 ± 0 8	87 5
1,500	(g) 7/10	25.7 ± 0 4	(h) 31 8 ± 1 1	(e) +6 2 ± 0 8	88 6
1,800	(i) 3/10	21 9 ± 0 5	31 0 ± 1 2	(e) +9 0 ± 1 0	86 4
FEMALE					
0	10/10	17.4 ± 0.5	26 3 ± 0.4	+8 9 ± 0 8	
600	10/10	18.2 ± 0 4	23 6 ± 0 3	(j) +5.4 ± 0 3	89 7
900	10/10	18.5 ± 0 5	25 0 ± 0 8	(j) +6 5 ± 0 7	95 1
1,000	10/10	18.8 ± 0.3	25 1 ± 0.3	(j) +6.3 ± 0 3	95 4
1,500	(k) 5/10	18.2 ± 0 4	26 0 ± 0 3	+7 4 ± 0 5	98 9
1,800	(l) 1/10	18 5 ± 0 4	26 0	(m) +6 0	98 9

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean, subsequent calculations based on those animals surviving to the end of the study.
(c) Mean group body weight change of the survivors ± standard error of the mean
(d) Week of death 13
(e) Significantly lower than vehicle controls by Williams' test, $P<0.05$
(f) Week of death: 13
(g) Week of death. 1, 1, 13
(h) Data from six animals weighed at the end of the study, the seventh animal was not weighed until necropsy and is not included in calculations of weight change or significance
(i) Week of death: 1, 1, 1, 1, 1, 1, 7
(j) Significantly lower than vehicle controls by Dunnett's test, $P<0.01$
(k) Week of death: 7, 8, 9, 13, 13
(l) Week of death: 1, 1, 1, 1, 8, 11, 13, 13, 13
(m) Data not analyzed because only one animal survived

1,500 mg/kg groups of females (27% and 33%) In male mice, the decreases were accompanied by decreases in both lymphocytes (26% decrease at the low dose to 33% at the two high doses) and neutrophils (69%-82% decreases). In females, there were also slight decreases in lymphocytes (up to 34%) and neutrophils (20%), but these were not statistically significant. The platelet count was significantly decreased in the 1,800 mg/kg male group but significantly increased in the 900, 1,000, and 1,500 mg/kg female groups Serum glutamic pyruvic transaminase (SGPT) values were not significantly affected by 1,4-dichlorobenzene in male and female mice However, the alkaline phosphatase value was increased 70% in the only two male mice examined in the 1,800 mg/kg group. Values for serum cholesterol, blood urea nitrogen, triglycerides, and total protein were not reported for female mice, since the sample size (less than 3) was insufficient to analyze most groups The concentration of serum triglycerides was significantly increased in male mice receiving 1,500 or 1,800 mg/kg Serum cholesterol concentrations were increased significantly in male mice receiving 900, 1,000, 1,500, or 1,800 mg/kg, total serum protein was significantly increased in male mice receiving 1,500 or 1,800 mg/kg Liver porphyrins were increased slightly in male mice at the 1,000-1,800 mg/kg doses (43%-83%) and in female mice at the 1,000 mg/kg dose (41%) However, these increases were relatively slight and of little biologic significance and do not indicate porphyria There was no evidence of an increase in the number of micronucleated red blood cells in blood smears from the mice in these 13-week studies (Appendix E, Table E6)

A second series of 13-week studies was conducted because high incidences of hepatocellular degeneration were observed in all dosed male and female mice. The decision to perform additional 13-week studies at lower doses was based on the absence of a no-effect level in the first studies and uncertainty as to whether the hepatocellular degeneration observed at 600 mg/kg would be life threatening.

SECOND THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 16). All deaths were attributed to gavage error. There was no significant change in body weight gain. Final mean body weights of male mice were 1%-8% greater than that of the vehicle controls. Final mean body weights of female mice ranged from 95% to 104% of those of vehicle controls. There was no apparent dose-response trend for either sex.

Centrilobular to midzonal hepatocytomegaly was observed at significantly increased incidences in male and female mice that received 675 or 900 mg/kg 1,4-dichlorobenzene (8/10 males and 4/10 females at 675 mg/kg and 9/10 males and 10/10 females at 900 mg/kg). Hepatocytomegaly was not observed in the vehicle controls or in the 337.5 mg/kg group of mice of either sex. The severity of the lesion was mild to moderate at 900 mg/kg and minimal to mild at 675 mg/kg.

Dose Selection Rationale: Because of the incidence and severity of histopathologic changes in the liver at 600 mg/kg in the first studies and at 675 mg/kg in the second studies, doses selected for mice for the 2-year studies were 300 and 600 mg/kg 1,4-dichlorobenzene to be administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control mice were comparable throughout the studies (Table 17 and Figure 3).

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	26.4 ± 0.5	32.9 ± 1.0	+6.5 ± 1.0	--
84.4	10/10	26.1 ± 0.7	34.4 ± 1.3	+8.3 ± 0.9	104.6
168.8	9/10	24.5 ± 0.9	34.0 ± 1.0	+9.0 ± 1.1	103.3
337.5	10/10	25.3 ± 0.8	33.2 ± 1.1	+7.9 ± 0.9	100.9
675	8/10	25.9 ± 0.3	35.5 ± 0.8	+9.6 ± 0.8	107.9
900	10/10	26.8 ± 0.6	34.5 ± 1.0	+7.7 ± 0.7	104.9
FEMALE					
0	8/10	22.3 ± 0.3	27.5 ± 0.6	+5.0 ± 0.7	--
84.4	8/10	21.4 ± 0.5	26.9 ± 0.8	+5.6 ± 0.4	97.8
168.8	9/10	22.6 ± 0.2	26.1 ± 0.6	+3.6 ± 0.4	94.9
337.5	9/10	22.5 ± 0.5	26.1 ± 0.6	+3.8 ± 0.4	94.9
675	9/10	22.6 ± 0.3	28.2 ± 0.4	+5.4 ± 0.4	102.5
900	10/10	23.9 ± 0.3	28.5 ± 0.6	+4.6 ± 0.5	103.6

(a) Number surviving/number initially in group; all deaths were related to gavage technique.
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean group body weight change of the survivors ± standard error of the mean

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	300 mg/kg Av. Wt. (grams)	300 mg/kg Wt. (percent of veh. controls)	300 mg/kg No. of Survivors	600 mg/kg Av. Wt. (grams)	600 mg/kg Wt. (percent of veh. controls)	600 mg/kg No. of Survivors
MALE								
0	25 6	50	25 3	99	50	24 9	97	50
1	27 2	50	26 9	99	50	26 3	97	50
2	28 2	50	27 9	99	50	28 0	99	50
3	29 5	50	29 0	98	50	29 2	99	50
4	30 5	50	30 0	98	50	30 3	99	50
5	29 8	50	30 7	103	50	30 5	102	50
6	31 3	50	30 9	99	50	30 1	96	50
7	31 8	50	32 0	101	50	30 8	97	50
8	32 5	50	32 4	100	49	32 1	99	50
9	33 5	50	31 8	95	49	32 1	96	50
10	32 9	50	33 1	101	49	32 7	99	50
11	35 5	47	34 8	98	44	33 1	93	44
12	35 0	47	34 4	98	42	33 2	95	42
16	35 9	47	35 2	98	42	35 2	98	42
20	36 3	47	36 8	101	42	35 5	98	42
24	38 1	47	38 1	100	42	37 7	99	42
28	40 5	47	38 5	95	41	38 7	96	42
33	40 8	47	40 0	98	41	40 3	99	42
37	41 5	47	41 5	100	40	41 5	100	42
41	41 8	46	41 5	99	40	41 7	100	42
46	42 5	46	42 5	100	40	42 6	100	42
51	41 9	46	40 8	97	40	41 4	99	42
55	42 2	46	42 4	100	40	43 6	103	42
59	44 0	45	44 3	101	40	45 0	102	42
64	45 3	45	43 7	96	40	46 2	102	42
68	43 2	44	44 4	103	40	44 6	103	42
72	44 1	44	44 3	100	40	45 2	102	42
77	42 7	43	42 3	99	40	43 9	103	42
81	42 9	43	43 4	101	39	43 4	101	42
85	42 8	43	42 7	100	39	42 6	100	41
89	42 0	40	42 4	101	39	41 7	99	38
93	41 5	36	43 1	104	36	40 3	97	34
98	40 3	32	41 8	104	34	39 8	99	31
103	39 5	28	41 7	106	32	39 3	99	31
FEMALE								
0	19 8	50	19 8	100	50	20 6	104	50
1	20 8	50	20 7	100	50	21 4	103	50
2	21 8	50	21 4	98	50	22 6	104	50
3	23 1	50	23 1	100	50	23 8	103	50
4	23 8	50	24 8	104	50	24 4	103	50
5	23 9	50	23 4	98	50	24 2	101	50
6	23 9	50	23 5	98	49	24 1	101	50
7	24 5	50	24 4	100	49	25 1	102	50
8	24 4	50	24 6	101	49	25 5	105	50
9	24 3	50	25 0	103	49	25 0	103	50
10	24 9	50	25 2	101	49	25 8	104	50
11	26 0	49	25 1	97	47	27 1	104	48
12	23 6	48	23 6	100	46	24 4	103	48
16	26 8	48	26 5	99	46	27 4	102	48
20	27 4	48	27 4	100	46	27 6	101	48
24	27 8	48	27 2	98	46	28 4	102	48
28	29 2	48	28 3	97	46	30 1	103	48
33	30 0	48	30 0	100	46	31 2	104	48
37	30 8	48	30 3	98	46	31 8	103	48
41	30 6	48	30 3	99	46	31 6	103	48
46	32 3	48	31 3	97	46	33 3	103	48
51	32 8	48	31 4	96	46	33 3	102	48
55	33 3	48	32 4	97	46	34 9	105	48
59	34 2	48	34 1	100	46	36 5	107	48
64	36 2	47	36 1	100	46	38 3	106	47
68	36 7	46	35 7	97	46	36 9	101	46
72	36 9	46	36 8	100	45	38 5	104	45
77	37 1	45	35 7	96	45	37 2	100	44
81	37 8	45	38 6	102	45	39 0	103	44
85	37 6	45	36 3	97	45	37 9	101	43
89	37 3	44	38 2	102	42	38 0	102	43
93	36 6	41	35 4	97	42	36 9	101	40
98	36 9	37	37 3	101	39	37 8	102	38
103	36 3	35	36 9	102	37	37 3	103	36

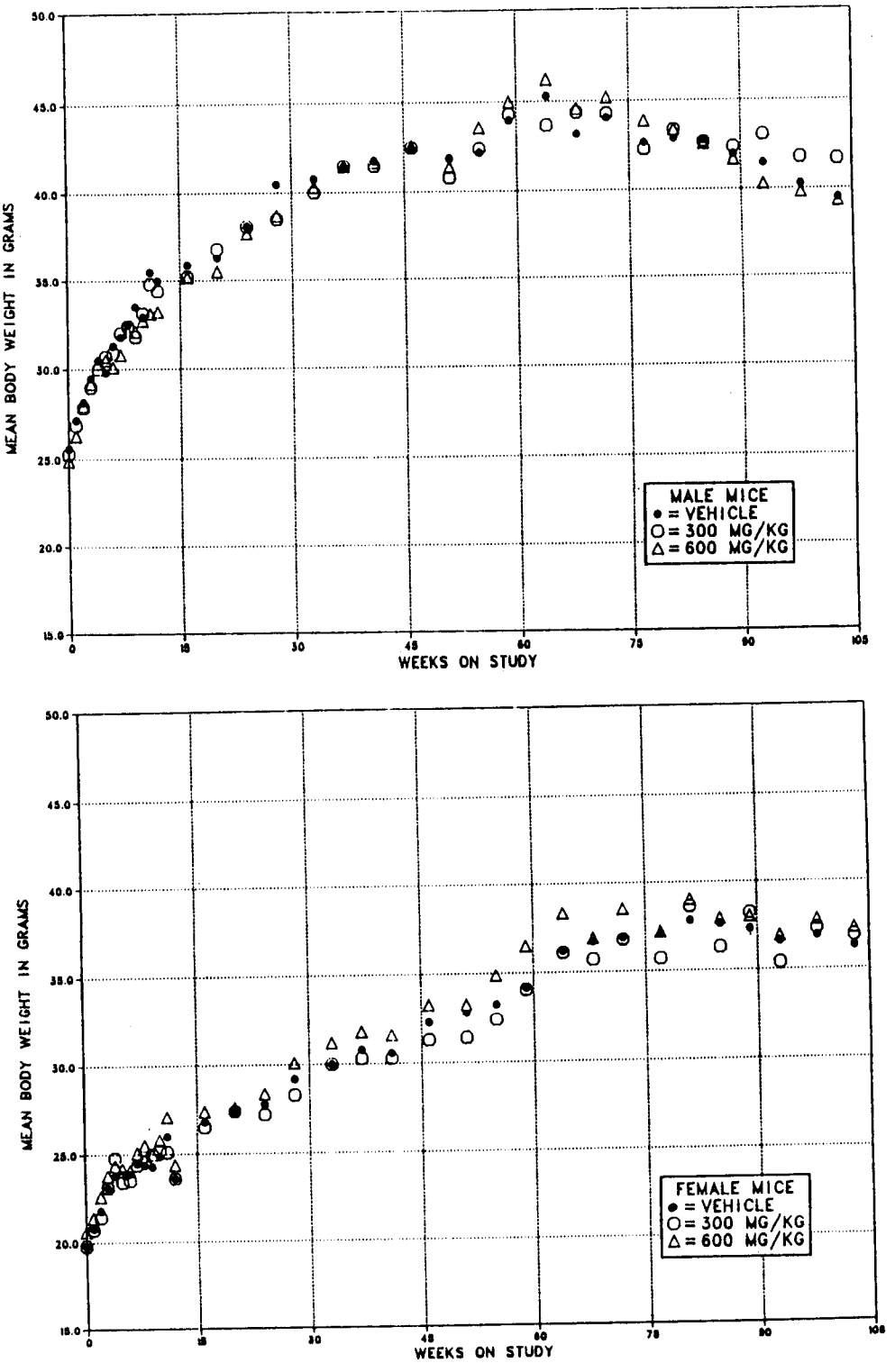

FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED 1,4-DICHLOROBENZENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 1,4-dichlorobenzene at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any group of either sex (Table 18).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, adrenal gland, thyroid gland, lung, hematopoietic system, and kidney.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	10	10
Accidentally killed (c)	3	8	9
Killed at termination	28	32	30
Died during termination period	0	0	1
Survival P values (d)	0.112	0.139	0.168
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	10	11
Accidentally killed (c)	3	4	3
Killed at termination	35	36	35
Died during termination period	0	0	1
Survival P values (d)	0.918	0.809	0.835

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) Gavage deaths
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

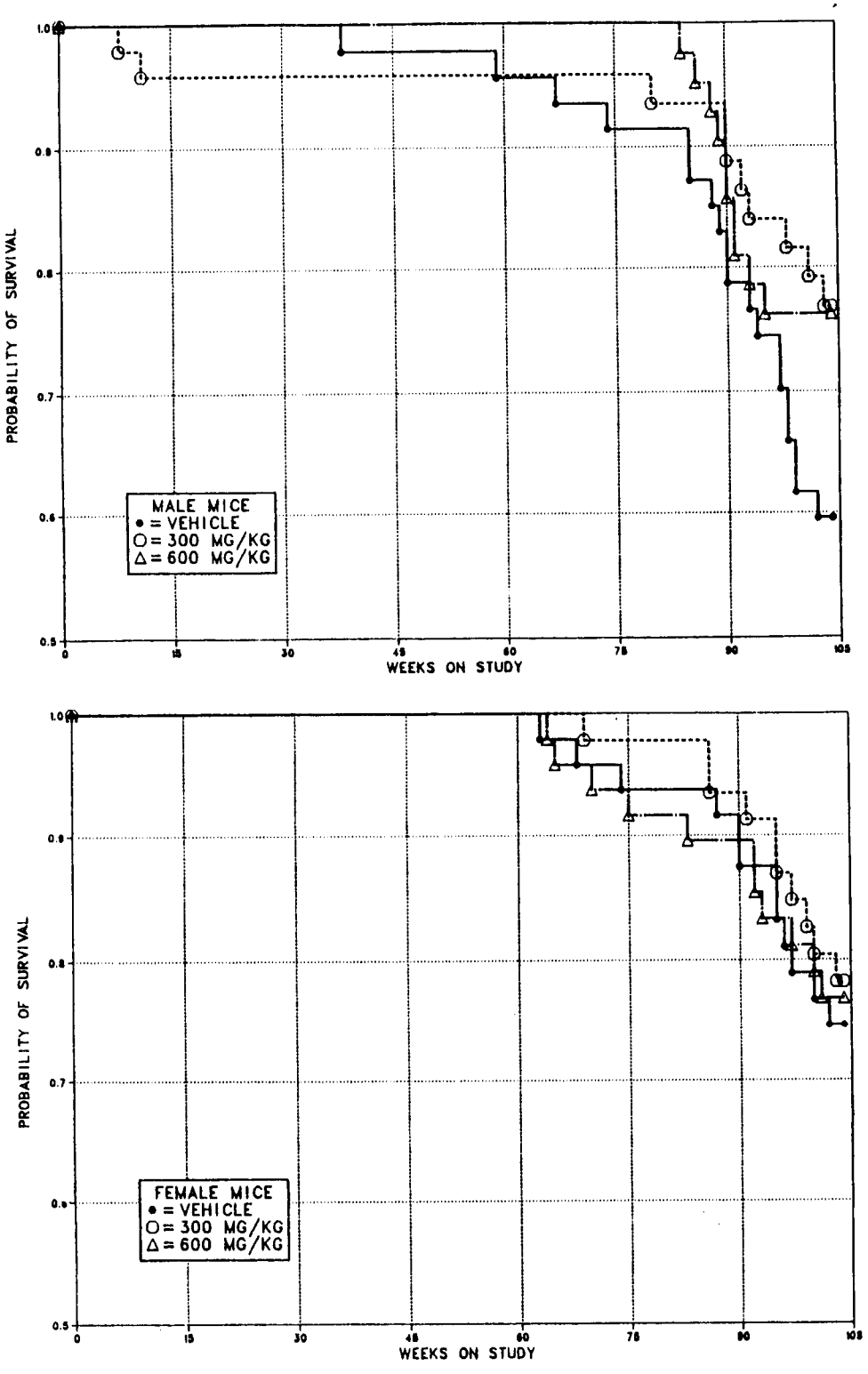

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 1,4-DICHLOROBENZENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: The incidences of hepatocellular degeneration with individual cell necrosis and cell size alteration (cytomegaly and karyomegaly) were increased in male and female mice receiving 1,4-dichlorobenzene (Table 19). The primary degenerative change was cellular swelling with clearing or vacuolation of the cytoplasm. Individual hepatocytes had pyknotic or karyorrhectic nuclei and condensed eosinophilic cytoplasm. Some necrotic hepatocytes formed globular eosinophilic masses in the sinusoids.

Hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas (combined) in male and female mice occurred with positive trends, and the incidences in the high dose groups were significantly greater than those in the vehicle controls (Table 20). The incidences of hepatocellular adenomas and adenomas or carcinomas (combined) in low dose male mice were also significantly greater than those in the vehicle controls. Hepatoblastomas occurred in four high dose male mice. Hepatoblastoma is a rare type of hepatocellular carcinoma (not seen in 1,091 vehicle controls) composed of small primitive cells with hyperchromatic nuclei and scant cytoplasm arranged in thick solid trabecular, pseudo-glandular, or rosette patterns.

Adrenal Gland: Pheochromocytomas or malignant pheochromocytomas (combined) in male mice occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in vehicle controls, and one malignant tumor was seen in this group (Table 21). The historical incidence of pheochromocytomas at this laboratory (5% ± 3%) is greater than that observed in the current study. However, the incidences of both medullary hyperplasia (Table 22) and focal hyperplasia of the adrenal gland capsule (vehicle control, 11/47, 23%; low dose, 21/48, 44%; high dose, 28/49, 57%) were also increased in dosed male mice.

TABLE 19. NUMBER OF MICE WITH LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

	Male			Female		
Lesion	Vehicle Control	300 mg/kg	600 mg/kg	Vehicle Control	300 mg/kg	600 mg/kg
Number of mice examined	50	49	50	50	48	50
Hepatocellular degeneration	0	36	39	0	8	36
Cell size alteration	0	38	40	0	4	27
Focal necrosis	1	35	37	1	4	30
Hepatocellular adenoma	5	13	16	10	6	21
Hepatocellular carcinoma	14	11	32	5	5	19
Hepatoblastoma	0	0	(a) 4	0	0	0

(a) All hepatoblastomas were observed in mice that had hepatocellular carcinomas.

TABLE 20. ANALYSIS OF LIVER TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	300 mg/kg	600 mg/kg
MALE			
Hepatocellular Adenoma			
Overall Rates	5/50 (10%)	13/49 (27%)	16/50 (32%)
Adjusted Rates	15.0%	39.4%	46.4%
Terminal Rates	3/28 (11%)	12/32 (38%)	13/31 (42%)
Week of First Observation	85	103	88
Life Table Tests	P=0.009	P=0.058	P=0.012
Incidental Tumor Tests	P=0.010	P=0.035	P=0.015
Hepatocellular Carcinoma			
Overall Rates	14/50 (28%)	11/49 (22%)	32/50 (64%)
Adjusted Rates	37.5%	28 5%	81.9%
Terminal Rates	7/28 (25%)	5/32 (16%)	24/31 (77%)
Week of First Observation	74	80	84
Life Table Tests	P<0.001	P=0 280N	P=0.002
Incidental Tumor Tests	P<0 001	P=0 570	P<0.001
Hepatocellular Adenoma or Carcinoma (b)			
Overall Rates	17/50 (34%)	22/49 (45%)	40/50 (80%)
Adjusted Rates	43.4%	57 6%	100.0%
Terminal Rates	8/28 (29%)	16/32 (50%)	31/31 (100%)
Week of First Observation	74	80	84
Life Table Tests	P<0.001	P=0 324	P<0.001
Incidental Tumor Tests	P<0.001	P=0.047	P<0.001
Hepatoblastoma (c)			
Overall Rates	0/50 (0%)	0/49 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	11.9%
Terminal Rates	0/28 (0%)	0/32 (0%)	3/31 (10%)
Week of First Observation			88
Life Table Tests	P=0.017	(d)	P=0.074
Incidental Tumor Tests	P=0.022	(d)	P=0.085
FEMALE			
Hepatocellular Adenoma			
Overall Rates	10/50 (20%)	6/48 (13%)	21/50 (42%)
Adjusted Rates	27.4%	16.7%	55.1%
Terminal Rates	9/35 (26%)	6/36 (17%)	19/36 (53%)
Week of First Observation	90	104	92
Life Table Tests	P=0.008	P=0.187N	P=0.017
Incidental Tumor Tests	P=0 006	P=0.197N	P=0.012
Hepatocellular Carcinoma			
Overall Rates	5/50 (10%)	5/48 (10%)	19/50 (38%)
Adjusted Rates	13 2%	12 6%	48.6%
Terminal Rates	3/35 (9%)	3/36 (8%)	16/36 (44%)
Week of First Observation	95	69	83
Life Table Tests	P<0.001	P=0.610N	P=0.002
Incidental Tumor Tests	P<0.001	P=0.578	P<0.001
Hepatocellular Adenoma or Carcinoma (e)			
Overall Rates	15/50 (30%)	10/48 (21%)	36/50 (72%)
Adjusted Rates	39.0%	25 9%	90.0%
Terminal Rates	12/35 (34%)	8/36 (22%)	32/36 (89%)
Week of First Observation	90	69	83
Life Table Tests	P<0 001	P=0.164N	P<0.001
Incidental Tumor Tests	P<0.001	P=0.200N	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) Historical incidence at study laboratory (mean ± SD) 50/150 (33% ± 4%); historical incidence in NTP studies: 357/1,091 (33% ± 10%)
(c) All hepatoblastomas were observed in animals also bearing hepatocellular carcinomas. No hepatoblastomas have been observed in corn oil gavage male mice (0/1,091) or in untreated control male mice (0/1,784). No hepatoblastomas were observed in corn oil gavage female mice (0/1,092) and in only 1/2,080 untreated female mice.
(d) No P value is reported because no tumors were observed in the 300 mg/kg and vehicle control groups
(e) Historical incidence at study laboratory (mean ± SD): 10/148 (7% ± 2%); historical incidence in NTP studies: 74/1,092 (7% ± 4%)

TABLE 21. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Medullary Hyperplasia			
Overall Rates	2/47 (4%)	4/48 (8%)	4/49 (8%)
Pheochromocytoma			
Overall Rates	0/47 (0%)	2/48 (4%)	3/49 (6%)
Adjusted Rates	0.0%	6.1%	9.3%
Terminal Rates	0/27 (0%)	1/32 (3%)	2/31 (6%)
Week of First Observation		103	95
Life Table Tests	P=0.094	P=0.277	P=0.136
Incidental Tumor Tests	P=0.028	P=0.181	P=0.063
Malignant Pheochromocytoma			
Overall Rates	0/47 (0%)	0/48 (0%)	1/49 (2%)
Pheochromocytoma (All Types) (a)			
Overall Rates	0/47 (0%)	2/48 (4%)	4/49 (8%)
Adjusted Rates	0.0%	6.1%	12.4%
Terminal Rates	0/27 (0%)	1/32 (3%)	3/31 (10%)
Week of First Observation		103	95
Life Table Tests	P=0.044	P=0.277	P=0.076
Incidental Tumor Tests	P=0.012	P=0.181	P=0.035

(a) Historical incidence at study laboratory (mean ± SD): 7/148 (5% ± 3%); historical incidence in NTP studies: 23/1,051 (2% ± 3%)

Thyroid Gland: Follicular cell hyperplasia was increased in male mice (vehicle control, 1/47, 2%; low dose, 4/48, 8%; high dose, 10/47, 21%) but not in female mice (Table 22). Follicular cell adenomas in female mice occurred with a significant positive trend. However, the incidence in the high dose group was not significantly greater than that in the vehicle controls.

Lung: The incidence of alveolar/bronchiolar carcinomas in low dose male mice was significantly greater than that in the vehicle controls; alveolar/bronchiolar carcinomas were not observed in the high dose or vehicle control groups (Table 23). The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) was not significantly greater in either dosed group than in the vehicle controls.

Hematopoietic System: The incidence of lymphoid hyperplasia of the mandibular lymph node was increased in dosed male and female mice (male: vehicle control, 1/46, 2%; low dose, 12/41, 29%; high dose, 10/47, 21%; female: 3/46, 7%; 8/43, 19%; 10/44, 23%).

Kidney: Increased incidences of nephropathy were observed in dosed male mice (vehicle control, 6/50, 12%; low dose, 12/50, 24%; high dose, 15/47, 32%) and to a much lesser extent in female mice (0/50; 3/47, 6%; 3/46, 7%). The nephropathy consisted primarily of degeneration of the cortical tubular epithelium with thickening of the tubular and glomerular basement membranes and increased interstitial collagen. Increased incidences of renal tubular regeneration were observed in dosed female mice (4/50, 8%; 7/47, 15%; 13/46, 28%) but not in males.

TABLE 22. ANALYSIS OF THYROID GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Follicular Cell Hyperplasia			
Overall Rates	8/48 (17%)	5/45 (11%)	9/46 (20%)
Follicular Cell Adenoma (a)			
Overall Rates	0/48 (0%)	0/45 (0%)	3/46 (7%)
Adjusted Rates	0.0%	0.0%	8.6%
Terminal Rates	0/35 (0%)	0/34 (0%)	3/35 (9%)
Week of First Observation			104
Life Table Tests	P=0.038	(b)	P=0.121
Incidental Tumor Tests	P=0.038	(b)	P=0.121

(a) Historical incidence at study laboratory (mean ± SD): 6/134 (4% ± 2%); historical incidence in NTP studies: 36/1,009 (4% ± 3%)
(b) No P value is reported because no tumors were observed in the 300 mg/kg and vehicle control groups.

TABLE 23. ANALYSIS OF LUNG LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Alveolar Epithelium Hyperplasia			
Overall Rates	1/50 (2%)	6/50 (12%)	2/50 (4%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	6/50 (12%)	8/50 (16%)	2/50 (4%)
Alveolar/Bronchiolar Carcinoma			
Overall Rates	0/50 (0%)	5/50 (10%)	0/50 (0%)
Adjusted Rates	0.0%	15.2%	0.0%
Terminal Rates	0/28 (0%)	4/32 (13%)	0/31 (0%)
Week of First Observation		103	
Life Table Tests	P=0.575N	P=0.047	(a)
Incidental Tumor Tests	P=0.558	P=0.028	(a)
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	6/50 (12%)	13/50 (26%)	2/50 (4%)
Adjusted Rates	17.8%	39.4%	6.5%
Terminal Rates	3/28 (11%)	12/32 (38%)	2/31 (6%)
Week of First Observation	88	103	104
Life Table Tests	P=0.116N	P=0.105	P=0.121N
Incidental Tumor Tests	P=0.150N	P=0.054	P=0.129N

(a) No P value is reported because no tumors were observed in the 600 mg/kg and vehicle control groups.
(b) Historical incidence at study laboratory (mean ± SD): 24/150 (16% ± 4%); historical incidence in NTP studies: 169/1,093 (15% ± 6%)

IV. DISCUSSION AND CONCLUSIONS

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IV. DISCUSSION AND CONCLUSIONS

Short-Term Studies (Rats)

Short-term studies were performed to identify the principal target organs, to characterize the prechronic toxicity of 1,4-dichlorobenzene in rats and mice, and to set doses for the 2-year studies. Clinical chemistry tests were performed to assist in the assessment of the toxicity of the compound on the liver, kidney, and hematopoietic system. Urinary and liver porphyrins were determined because a related compound, hexachlorobenzene, is known to produce a disease known as hepatic porphyria in both humans and rodents (Ockner and Schmid, 1961).

The kidney and liver have been reported to be the principal sites affected when 1,4-dichlorobenzene is administered to rats and mice in short-term studies (Hollingsworth et al., 1956). The hepatotoxicity of 1,4-dichlorobenzene is less than that of 1,2-dichlorobenzene when administered at equivalent doses (Brodie et al., 1971; Reid and Krishna, 1973). In the current 13-week studies, renal toxicity was more common in male rats than in female rats dosed with 1,4-dichlorobenzene. The renal lesion was characterized by multifocal degeneration or necrosis of the renal cortical tubular epithelial cells at doses of 1,200 mg/kg or more and renal tubular degeneration at doses of 600 mg/kg or more, with some indication of a slight increase in the incidence of tubular regeneration at 300 mg/kg. There was an increase in the number and size of eosinophilic droplets in the cytoplasm of epithelial cells of the proximal convoluted tubules. Linder et al. (1980) also reported a dose-related increase in hyaline droplets in male rats given another chlorobenzene, pentachlorobenzene, in the diet at concentrations of 125, 250, 500, or 1,000 ppm for 100 days. The increase was seen in 8/10 male rats at the 125-ppm level but was even more pronounced at higher levels. In contrast, hyaline droplets were observed in only 1/10 females fed 1,000 ppm for 180 days and were not observed at lower doses in females. The increase in hyaline droplets in male rats in these two studies is similar to that reported in these cells after exposure of male rats to light hydrocarbons (Phillips and Cockrell, 1984). Increases in the kidney weight to brain weight ratio were another indication of kidney damage observed in male rats in the present study. Moreover, blood urea nitrogen levels were increased in male rats dosed with 900 mg/kg or more.

1,4-Dichlorobenzene increased the liver weight to brain weight ratio at doses of 900 mg/kg or more in male and female rats, whereas degeneration and necrosis of hepatocytes were seen at doses of 1,200 mg/kg or more. Several clinical chemistry parameters were affected, which may reflect the hepatic effects of this compound. In male rats, the serum cholesterol level was increased at doses of 600 mg/kg or more, whereas the serum triglycerides were reduced by doses of 300 mg/kg or more. In female rats, serum cholesterol was affected at doses of 900 mg/kg or more. However, SGPT was not affected in either male or female rats, and alkaline phosphatase was increased only in female rats receiving 1,200 mg/kg. Although female rats were generally less sensitive to 1,4-dichlorobenzene than were male rats, some deaths occurred at 900 mg/kg in both male and female rats.

Expanded hematologic studies were performed because Girard et al. (1969) reported the development of leukemia in five persons exposed to 1,2-dichlorobenzene or 1,4-dichlorobenzene used as a solvent for other chemicals or to chlorinated benzene mixtures. Two of the patients were diagnosed as having chronic lymphoid leukemia, two as having acute myeloblastic leukemia, and one as having a myeloproliferative syndrome. Girard et al. also reported two cases of severe anemia associated with exposure to monochlorobenzene or trichlorobenzene. Moreover, Hallowell (1959) reported two incidents of hemolytic anemia in humans exposed to 1,4-dichlorobenzene at large doses. In the present 13-week study, 1,4-dichlorobenzene produced a mild microcytic anemia in male rats. The effect was most pronounced at the high dose. None of these hematologic changes occurred in female rats, although the mean corpuscular volume was decreased in females at doses of 600 mg/kg or more. The white blood cell count was not affected in either sex at any dose. The hematologic changes were modest and occurred in male rats at toxic doses that also depressed body weight gain. Therefore, the results of these studies indicate that 1,4-dichlorobenzene produces only minimal hematologic changes in rats and do not suggest any effect on white blood cells in this species.

Short-Term Studies (Mice)

Two 13-week studies were performed in mice at doses of 600-1,800 mg/kg and 85-900 mg/kg. In the first studies, survival was decreased in both sexes at doses of 1,500 mg/kg or more. Hepatocellular degeneration was observed histologically in males and females at doses of 600-1,800 mg/kg, but kidney damage was not observed. Liver weight to brain weight ratios were increased at doses of 900 mg/kg or more. The white blood cell count was reduced significantly for all groups of dosed male mice and for female mice at 1,000 or 1,500 mg/kg. These effects were accompanied by decreases in neutrophils and lymphocytes. The hematocrit and red blood cell count were not altered in either sex. Serum cholesterol concentrations were increased in males at doses of 900 mg/kg or more, and serum triglycerides were increased in males receiving 1,500 mg/kg or more. These changes are consistent with the hepatic effects of this compound. These parameters were not measured in female mice due to insufficient serum sample size. In the second studies, hepatocytomegaly was observed in male and female mice at doses of 675 or 900 mg/kg but not at 375 mg/kg. The hepatocellular lesion was rated as minimal to mild at 675 mg/kg and mild to moderate at 900 mg/kg. On the basis of these data, doses of 300 and 600 mg/kg were selected for the 2-year studies.

Although there is clear-cut evidence that hexachlorobenzene produces porphyria (Ockner and Schmid, 1961; Carlson, 1977), several laboratories have reported that many less chlorinated benzenes (1,4-dichlorobenzene, 1,2,4-trichlorobenzene, and pentachlorobenzene) do not appear to produce porphyria in rats or mice (Carlson, 1977; Linder et al., 1980). In the present studies, 1,4-dichlorobenzene did not cause hepatic porphyria when administered for 13 weeks to rats at doses of 300-1,500 mg/kg or when administered to mice for 13 weeks at 600-1,800 mg/kg. Similarly, the NTP (1985b) recently reported that 1,2-dichlorobenzene did not cause hepatic porphyria in rats and mice at doses of up to 500 mg/kg per day for 13 weeks. Small increases in levels of urinary porphyrins (rats) (1.5-fold to sixfold) or hepatic porphyrins (mice) (40%-80%) were observed in the present studies. However, changes of this magnitude are considered to be physiologic rather than pathologic changes. In comparison, hexachlorobenzene administered in the diet at 300 ppm to female Sprague-Dawley rats for 4 months increased tissue porphyrin levels from 1.0 ± 0.1 to 385 ± 85 µg/g and urinary uroporphyrin excretion from 1.4 ± 0.2 µg/24 hours to 383 ± 63 µg/24 hours (both increases are more than hundredfold) (Goldstein et al., 1978).

Two-Year Studies (Rats)

Doses of 150 and 300 mg/kg 1,4-dichlorobenzene were selected for the 2-year studies for male rats. These doses were based primarily on the renal toxicity observed in the 13-week study in males and hepatotoxicity at higher doses in both sexes. Although the incidence of renal tubular degeneration in male rats in the first 13-week study was increased at 300 mg/kg, there was only an equivocal increase in the severity and no increase in the incidence of renal tubular degeneration in male rats at this dose in the second 13-week study, and at 150 mg/kg, there were no detectable effects on the kidney in the second study. Female rats were generally less sensitive to 1,4-dichlorobenzene than were male rats in the 13-week study, and no kidney lesions were observed at any dose. However, some deaths occurred in females at 900 mg/kg, and degeneration and necrosis of hepatocytes as well as body weight loss were observed at 1,200 mg/kg. Therefore, the doses selected for the 2-year study for female rats were 300 and 600 mg/kg.

In the 2-year study, survival of male rats dosed with 300 mg/kg 1,4-dichlorobenzene was significantly lower than that of vehicle controls after week 97 ($P=0.005$) (see Table 9 and Figure 2), and body weights were 5%-8% lower than that of vehicle controls after week 38 (see Figure 1). Survival of low dose male rats and dosed female rats was similar to that of the vehicle controls. However, body weights of female rats dosed with 600 mg/kg were lower than those of the vehicle controls after week 55.

1,4-Dichlorobenzene increased the incidence of nephropathy in high dose (600 mg/kg) female rats (vehicle control, 43%; low dose, 64%; high dose, 84%) (see Table 10) and increased the severity of the lesion in dosed male rats. All

groups of dosed male rats had marked increases in mineralization of the collecting tubules of the renal medulla (8%; 92%; 94%) and epithelial hyperplasia of the renal pelvis (2%; 60%; 62%). Incidences of renal tubular cell adenocarcinomas were clearly increased in dosed male rats (2%; 6%; 14%) (see Tables 10 and 11). The increases occurred with a significant ($P=0.005$) positive trend, and the incidence in the high dose group was significantly ($P=0.011$) greater than that in the vehicle controls by the life table test. These malignant tumors are uncommon in male F344/N rats, having been diagnosed in only 4/1,098 (0.4%) corn oil gavage controls in previous NTP studies (Table A4a). Two of the tumors in low dose male rats and two of the tumors in high dose male rats were grossly visible at necropsy. The increase in this neoplasm is considered to have been produced by the administration of the compound. Administration of 1,4-dichlorobenzene did not produce renal neoplasms in female rats in the present study. The increase in hyperplasia of the parathyroid gland observed in male rats (10%; 31%; 53%) in the present 2-year study was not noted in female rats. The hyperplasia of the parathyroid gland is probably related to a decrease in functional renal mass, a subsequent alteration in serum phosphate and calcium excretion by the kidney, and stimulation of the parathyroid gland to release parathyroid hormone (Anderson, 1978).

The spectrum of renal toxicity in male rats given 1,4-dichlorobenzene by gavage for 13 weeks and 2 years is similar to that of male rats exposed to gasoline vapors, related petroleum naphthas, light hydrocarbons consisting of paraffins, cycloparaffins, or alkyl aromatic hydrocarbons, and decalin (Mehlman et al., 1984). Long-term administration of a number of these compounds to male rats produces renal tubular cell adenocarcinomas. Degeneration of epithelium in proximal convoluted tubules, regeneration, and dilated tubules filled with granular proteinaceous material were reported in male rats exposed to light hydrocarbon compounds in short-term inhalation studies (Phillips and Cockrell, 1984). The characteristic early lesion consisted of an accumulation of hyaline droplets in epithelial cells that were demonstrated to be phagolysosomes filled with amorphous electron-dense material. The hyaline droplets formed within tubular cells of male rats following exposure to decalin were reported to be primarily α-2-microglobulin, a specific protein produced in the liver under the influence of testosterone (Trump et al., 1984). Whether this protein plays a role in the pathogenesis of the chronic lesions associated with administration of these hydrocarbons or 1,4-dichlorobenzene is unknown. Administration of pentachlorobenzene in the diet also produced a dramatic increase in the number of hyaline droplets in the kidneys of male but not of female rats (Linder et al., 1980).

Mononuclear cell leukemia occurred with a marginally increased incidence in high dose male rats (22%) when compared with concurrent vehicle controls (10%), but the incidence is only slightly greater than the average historical incidence in three other corn oil vehicle control groups at this laboratory (17% ± 3%) (Table A4b). No increase in mononuclear cell leukemia was observed in female rats in the present study (vehicle control, 30%; low dose, 20%; high dose, 18%). In male rats, mononuclear cell leukemia is a common tumor originating in the spleen, and it occurs with a wide range of incidences. Therefore it is doubtful whether the increase in the incidence of this tumor in high dose male rats in the present study is related to the administration of 1,4-dichlorobenzene.

Two-Year Studies (Mice)

In mice, survival and body weights in the 2-year studies were not affected by administration of 300 or 600 mg/kg 1,4-dichlorobenzene. 1,4-Dichlorobenzene increased the incidences of nonneoplastic liver lesions in male and female mice. The lesions included alterations in cell size, degeneration and single-cell necrosis of hepatocytes, and cytomegaly and karyomegaly. 1,4-Dichlorobenzene also increased the incidences of nephropathy in male mice and renal tubular regeneration in female mice.

1,4-Dichlorobenzene increased the incidences of hepatocellular neoplasms in both male and female mice. There was an increase in the number of hepatocellular adenomas in dosed male (vehicle control, 10%; low dose, 26%; high dose, 32%) and high dose female mice (20%; 13%; 42%) accompanied by a positive dose-response trend.

There was also an increase in the incidence of hepatocellular carcinomas in both high dose male (28%; 22%; 64%) and female mice (10%; 10%; 38%) with a positive dose-response trend. Hepatoblastomas were observed in four high dose male mice but not in any other group. These rare tumors have been observed historically in 0/1,091 vehicle control male mice (Table C4b) and 0/1,784 untreated control male mice. Another chlorinated benzene, monochlorobenzene, increased the incidence of neoplastic nodules of the liver in male rats, although it did not increase the incidence of hepatic tumors in either sex of mice (NTP, 1985a). Hexachlorobenzene has been reported to increase the incidence of hepatomas in male and female hamsters (Cabral et al., 1977), male and female outbred Swiss mice (Cabral et al., 1979), and female Agus rats (male rats were not studied) (Smith and Cabral, 1980).

There was a positive dose-response trend for adrenal gland pheochromocytomas (five benign and one malignant) in male mice, and the incidence in the high dose group was greater than that of concurrent vehicle controls (vehicle control, 0%; low dose, 4%; high dose, 8%). Although the incidence of pheochromocytomas in the high dose males is only slightly greater than the historical rate for this tumor in vehicle control male mice in this laboratory (5% ± 3%) or in all laboratories (2% ± 3%), the marginal increase in adrenal gland medullary hyperplasia (4%; 8%; 8%) tends to provide some support for the positive dose-response trend for pheochromocytomas. Focal hyperplasia of the adrenal gland capsule was also observed in dosed male mice (23%; 44%; 57%).

A positive dose-response trend for follicular cell adenomas of the thyroid gland was observed in dosed female mice, but the incidence was not significantly greater in the high dose group than in the vehicle controls. 1,4-Dichlorobenzene also increased the incidences of hyperplasia of the thyroid gland in dosed male but not female mice (see Table 22). Hexachlorobenzene has been reported to produce alveolar adenomas of the thyroid gland in male hamsters (Cabral et al., 1977). Therefore, the marginal effect of 1,4-dichlorobenzene on this organ may have biologic significance.

Mutagenicity

1,4-Dichlorobenzene has been tested for mutagenic activity by the National Toxicology Program as well as by a number of other laboratories. Results from most of these short-term in vitro tests indicate that 1,4-dichlorobenzene is not mutagenic or genotoxic to either bacterial or mammalian cells in culture, although it does appear to produce chromosomal aberrations in plants. It has been shown that monochlorobenzene, 1,2-dichlorobenzene, and 1,2,4-trichlorobenzene do not induce DNA repair in rat hepatocytes (Shimada and Williams, unpublished data), but no reports of effects of 1,4-dichlorobenzene on DNA repair in rat hepatocytes in vitro are available. Zapata-Gayon et al. (1982) reported an increase in chromosomal aberrations in peripheral blood from humans accidentally exposed to 1,2-dichlorobenzene. However, in vivo cytogenetic and dominant lethal studies with rodents failed to corroborate clastogenic effects of 1,4-dichlorobenzene in laboratory animals. The NTP in vivo cytogenetics study indicated no increase in micronucleated cells in mice in the 13-week studies even at toxic doses (Table E6). Thus, the carcinogenic activity of 1,4-dichlorobenzene cannot be adequately predicted on the basis of available genotoxicity data. Since most of the data suggest that chlorinated benzenes are not genotoxic, 1,4-dichlorobenzene may produce tumors by other mechanisms. Smith (1985) has presented preliminary data indicating that hexachlorobenzene may act as a promoter of liver tumors in rats. 1,4-Dichlorobenzene may produce liver tumors in mice by a similar mechanism.

Data Audit

The experimental and tabulated data for the NTP Technical Report on 1,4-dichlorobenzene were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements. As summarized in Appendix N, the audit revealed no major problems with the conduct of the studies or with the collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of these studies.

IV. DISCUSSION AND CONCLUSIONS

Conclusions

Under the conditions of these 2-year gavage studies, 1,4-dichlorobenzene produced *clear evidence of carcinogenicity** for male F344/N rats, as shown by an increased incidence of renal tubular cell adenocarcinomas. There was *no evidence of carcinogenicity* for female F344/N rats receiving doses of 300 or 600 mg/kg. There was *clear evidence of carcinogenicity* for both male and female B6C3F$_1$ mice, as shown by increased incidences of hepatocellular carcinomas and hepatocellular adenomas. Marginal increases were observed in the incidences of pheochromocytomas of the adrenal gland in male mice. Nonneoplastic effects in the kidney of male and female rats, in the liver of male and female mice, and in the thyroid gland and adrenal gland of male mice were also associated with the administration of 1,4-dichlorobenzene.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
Squamous cell carcinoma	1 (2%)		
Trichoepithelioma	1 (2%)		1 (2%)
Sebaceous adenoma	1 (2%)		1 (2%)
Sebaceous adenocarcinoma	1 (2%)		
Keratoacanthoma		4 (8%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	
Fibrosarcoma	2 (4%)		
Lipoma	1 (2%)	1 (2%)	
Rhabdomyosarcoma	1 (2%)		
Fibroadenoma			1 (2%)
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma		1 (2%)	
C-cell carcinoma, metastatic		1 (2%)	
Sebaceous adenocarcinoma, metastatic	1 (2%)		
Liposarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	5 (10%)	7 (14%)	11 (22%)
#Spleen	(49)	(48)	(49)
Fibroma			1 (2%)
#Splenic capsule	(49)	(48)	(49)
Mesothelioma, NOS	1 (2%)		
#Mandibular lymph node	(44)	(48)	(39)
Malignant lymphoma, lymphocytic type		1 (2%)	
CIRCULATORY SYSTEM			
#Spleen	(49)	(48)	(49)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
#Liver	(50)	(49)	(50)
Neoplastic nodule	1 (2%)	2 (4%)	
Hepatocellular carcinoma	1 (2%)		
#Pancreas	(50)	(48)	(46)
Acinar cell adenoma	4 (8%)	9 (19%)	5 (11%)
Acinar cell carcinoma			1 (2%)
#Forestomach	(49)	(47)	(45)
Squamous cell papilloma			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma			1 (2%)
Tubular cell adenocarcinoma	1 (2%)	3 (6%)	7 (14%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(49)	(49)
Adenoma, NOS	9 (20%)	10 (20%)	7 (14%)
#Adrenal	(50)	(49)	(50)
Cortical adenoma	2 (4%)		
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma	11 (22%)	17 (35%)	11 (22%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(48)	(45)
Follicular cell adenoma	1 (2%)	1 (2%)	1 (2%)
Follicular cell carcinoma	1 (2%)	2 (4%)	1 (2%)
C-cell adenoma	9 (19%)	6 (13%)	4 (9%)
C-cell carcinoma	2 (4%)	2 (4%)	2 (4%)
#Parathyroid	(42)	(42)	(38)
Adenoma, NOS	1 (2%)	1 (2%)	2 (5%)
#Pancreatic islets	(50)	(48)	(46)
Islet cell adenoma	2 (4%)	2 (4%)	1 (2%)
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
Fibroadenoma	1 (2%)	1 (2%)	4 (8%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS		3 (6%)	1 (2%)
Adenocarcinoma, NOS			1 (2%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	44 (88%)	41 (82%)	47 (94%)
NERVOUS SYSTEM			
#Brain	(49)	(48)	(48)
Granular cell tumor, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*Ear canal	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Cervical vertebra other	(50)	(50)	(50)
Osteoma	1 (2%)		
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		2 (4%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Mesothelioma, malignant			2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	7	11
Moribund sacrifice	5	7	15
Terminal sacrifice	32	31	20
Dosing accident	3	5	4
Accidentally killed, nda	4		
TUMOR SUMMARY			
Total animals with primary tumors**	49	43	49
Total primary tumors	109	120	121
Total animals with benign tumors	46	42	48
Total benign tumors	89	99	92
Total animals with malignant tumors	16	14	23
Total malignant tumors	17	18	27
Total animals with secondary tumors##	1	2	1
Total secondary tumors	1	2	1
Total animals with tumors uncertain-- benign or malignant	2	3	2
Total uncertain tumors	3	3	2

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: VEHICLE CONTROL

ANIMAL NUMBER	020	043	036	015	026	050	003	024	037	038	039	040	010	021	034	044	049	012	001	002	004	005	008	007	008
WEEKS ON STUDY	023	046	050	065	066	068	074	087	089	089	089	089	091	093	093	098	099	103	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
Trichoepithelioma																									
Sebaceous adenoma									X																
Sebaceous adenocarcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma		X																							
Lipoma																									
Rhabdomyosarcoma	X																								
Neurofibrosarcoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenocarcinoma, metastatic									X																
Trachea	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Lymph nodes	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Thymus	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma												X													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X	X				X									X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																				X					
Pheochromocytoma										X								X	X					X	X
Pheochromocytoma, malignant						X																			
Thyroid	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma									X																
C-cell adenoma													X			X	X							X	
C-cell carcinoma																									
Parathyroid	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma														X											
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	N	+	+	N	N	+	N	N	+	+	N	N	N	+	N	+	+	N	N	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N
Osteoma																			X						
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell				X			X								X										

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0 0 9	0 1 1	0 1 3	0 1 4	0 1 6	0 1 7	0 1 8	0 1 9	0 2 2	0 2 3	0 2 5	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 5	0 4 1	0 4 2	0 4 5	0 4 6	0 4 7	0 4 8	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																			X							1
Trichoepithelioma																										1
Sebaceous adenoma								X																		1
Sebaceous adenocarcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																		X								2
Lipoma																				X						1
Rhabdomyosarcoma																										1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous adenocarcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesothelioma, NOS		X																								1
Lymph nodes	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	–	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma												X														1
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																X										1
Hepatocellular carcinoma																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma		X							X									X								4
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS											X			X				X	X							9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																		X								2
Pheochromocytoma										X		X		X								X		X	X	11
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma										X																1
Follicular cell carcinoma																										1
C-cell adenoma	X			X					X					X								X				9
C-cell carcinoma								X	X																	2
Parathyroid	+	+	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	+	+	+	42
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma											X															2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	N	+	+	+	N	N	N	+	+	+	+	+	+	N	+	N	+	+	N	+	N	*50
Fibroadenoma																					X					1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	44
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS		X																								1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell														X		X										5

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: LOW DOSE

ANIMAL NUMBER	0046	0026	0113	0224	0225	0006	0336	0111	0448	0003	0311	0337	0338	0001	0334	0440	0115	0330	0339	0002	0004	0005	0007	0008	0009
WEEKS ON STUDY	037	038	039	042	044	050	057	058	063	070	079	084	085	090	091	096	101	101	101	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma																		X							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Lipoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
C cell carcinoma, metastatic																						X			
Liposarcoma, metastatic											X														
Trachea	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
Thymus	−	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																						X			
Bile duct	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																					X				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																		X				X			
Urinary bladder	−	+	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS										X			X												X
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X			X		X				X	X	X	
Thyroid	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																							X		
C cell adenoma														X										X	X
C cell carcinoma																						X			
Parathyroid	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adenoma, NOS																									X
Pancreatic islets	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	N	N	N	N	N	N	+	N	+	N	+	+	N	N	+	N	+	+	+
Fibroadenoma																					X				
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																X									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																	X								
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell							X						X					X		X			X		

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

ANIMAL NUMBER	010	012	014	016	017	018	019	020	021	022	023	027	028	029	032	035	038	041	042	043	044	045	047	049	050	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma						X																				1
Keratoacanthoma															X							X	X			4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
C-cell carcinoma, metastatic																										1
Liposarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma															X											1
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, lymphocytic type			X																							1
Thymus	+	+	+	–	+	–	–	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule												X														2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma				X				X						X	X						X	X	X			9
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																					X					3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X			X				X		X	X						X							X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X		X	X			X	X				X				X			X			X		X	X	17
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																X										1
Follicular cell carcinoma																		X								2
C cell adenoma										X											X	X				6
C-cell carcinoma			X																							2
Parathyroid	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	42
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma					X					X																2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	N	N	+	N	+	N	N	N	N	+	N	+	N	+	+	+	+	N	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/chtoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS										X								X	X							3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granular cell tumor, NOS																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma										X																1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X												X													7

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: HIGH DOSE

ANIMAL NUMBER	0034	0155	0188	0007	0441	0009	0221	0455	0422	0377	0333	0191	0277	0466	0330	0222	0101	0177	0133	0331	0220	0225	0266	0088	0488
WEEKS ON STUDY	0003	0046	0601	0661	0661	0663	0711	0711	0733	0744	0777	0788	0788	0811	0822	0844	0855	0855	0900	0902	0903	0944	0977	0988	0998
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Trichoepithelioma																									
Sebaceous adenoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	–	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lymph nodes	+	+	–	+	–	+	–	+	+	–	+	+	–	+	+	–	+	+	+	–	+	–	+	+	+
Thymus	+	–	+	–	–	–	+	+	+	–	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																					X				
Acinar cell carcinoma																								X	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Small intestine	+	+	–	–	+	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	–	–	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																			X						
Tubular cell adenocarcinoma		X																							X
Urinary bladder	+	+	+	–	+	–	–	+	+	–	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X		X					X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																				X					
Follicular cell carcinoma																									
C cell adenoma								X				X													
C cell carcinoma																									
Parathyroid	–	+	+	+	+	–	–	+	+	–	+	+	+	–	+	–	–	+	+	+	–	+	+	+	+
Adenoma, NOS																								X	
Pancreatic islets	+	+	+	+	+	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma												X													
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	N	N	N	N	+	+	N	N	N	N	N	+	N	N	+	+	+	+	N	+
Adenocarcinoma, NOS																									
Fibroadenoma					X																				
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, NOS																								X	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Tubular cell adenocarcinoma, metastatic																									
Mesothelioma, malignant								X																	
Leukemia, mononuclear cell									X	X		X		X				X			X	X	X		

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

ANIMAL NUMBER	0161	0006	0110	0111	0444	0002	0003	0004	0005	0112	0114	0234	0244	0288	0299	0325	0355	0366	0388	0399	0400	0433	0477	0499	0500	TOTAL:
WEEKS ON STUDY	101	102	103	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																			X							1
Trichoepithelioma															X											1
Sebaceous adenoma								X																		1
Keratoacanthoma	X														X											2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma												X														1
Lymph nodes	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	39
Thymus	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Acinar cell adenoma			X	X	X			X																		5
Acinar cell carcinoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Tubular cell adenocarcinoma		X		X	X				X					X												7
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X					X							X												7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X												X	X	X	X		X	X	X				X	X	11
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																										1
Follicular cell carcinoma																X										1
C cell adenoma							X									X										4
C-cell carcinoma						X						X														2
Parathyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	38
Adenoma, NOS								X																		2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma																										1
Islet cell carcinoma														X												1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	+	+	+	N	N	+	N	N	N	+	+	+	+	+	+	+	+	N	N	N	+	*50
Adenocarcinoma, NOS							X																			1
Fibroadenoma				X		X														X						4
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																						X				1
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS								X									X									2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Tubular cell adenocarcinoma, meta		X																								1
Mesothelioma, malignant					X																					2
Leukemia, mononuclear cell				X									X										X			11

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	150 mg/kg	300 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	0.0%	12.3%	8.8%
Terminal Rates (c)	0/32 (0%)	3/31 (10%)	1/20 (5%)
Week of First Observation		101	101
Life Table Tests (d)	P=0.116	P=0.062	P=0.162
Incidental Tumor Tests (d)	P=0.210	P=0.055	P=0.254
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.059	P=0.247
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.9%	0.0%	0.0%
Terminal Rates (c)	1/32 (3%)	0/31 (0%)	0/20 (0%)
Week of First Observation	46		
Life Table Tests (d)	P=0.051N	P=0.131N	P=0.172N
Incidental Tumor Tests (d)	P=0.029N	P=0.097N	P=0.128N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	7.9%	2.9%	0.0%
Terminal Rates (c)	1/32 (3%)	0/31 (0%)	0/20 (0%)
Week of First Observation	46	101	
Life Table Tests (d)	P=0.086N	P=0.316N	P=0.172N
Incidental Tumor Tests (d)	P=0.036N	P=0.282N	P=0.128N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	11/50 (22%)
Adjusted Rates (b)	12.8%	19.6%	32.1%
Terminal Rates (c)	2/32 (6%)	4/31 (13%)	2/20 (10%)
Week of First Observation	65	57	73
Life Table Tests (d)	P=0.025	P=0.349	P=0.040
Incidental Tumor Tests (d)	P=0.221	P=0.331	P=0.300
Cochran-Armitage Trend Test (d)	P=0.063		
Fisher Exact Test (d)		P=0.380	P=0.086
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	4/50 (8%)	9/48 (19%)	5/46 (11%)
Adjusted Rates (b)	11.8%	29.0%	20.1%
Terminal Rates (c)	3/32 (9%)	9/31 (29%)	1/20 (5%)
Week of First Observation	91	104	93
Life Table Tests (d)	P=0.181	P=0.100	P=0.282
Incidental Tumor Tests (d)	P=0.343	P=0.097	P=0.571
Cochran-Armitage Trend Test (d)	P=0.379		
Fisher Exact Test (d)		P=0.102	P=0.447
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	9/48 (19%)	6/46 (13%)
Adjusted Rates (b)	11.8%	29.0%	23.1%
Terminal Rates (c)	3/32 (9%)	9/31 (29%)	1/20 (5%)
Week of First Observation	91	104	93
Life Table Tests (d)	P=0.113	P=0.100	P=0.181
Incidental Tumor Tests (d)	P=0.265	P=0.097	P=0.474
Cochran-Armitage Trend Test (d)	P=0.270		
Fisher Exact Test (d)		P=0.102	P=0.318

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	3.1%	9.2%	25.7%
Terminal Rates (c)	1/32 (3%)	2/31 (6%)	2/20 (10%)
Week of First Observation	104	101	46
Life Table Tests (d)	P=0.005	P=0.301	P=0.011
Incidental Tumor Tests (d)	P=0.022	P=0.278	P=0.037
Cochran-Armitage Trend Test (d)	P=0.017		
Fisher Exact Test (d)		P=0.309	P=0.030
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	3.1%	9.2%	28.0%
Terminal Rates (c)	1/32 (3%)	2/31 (6%)	2/20 (10%)
Week of First Observation	104	101	46
Life Table Tests (d)	P=0.002	P=0.301	P=0.006
Incidental Tumor Tests (d)	P=0.012	P=0.278	P=0.022
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.309	P=0.015
Pituitary Gland: Adenoma			
Overall Rates (a)	9/45 (20%)	10/49 (20%)	7/49 (14%)
Adjusted Rates (b)	25.8%	29.5%	25.1%
Terminal Rates (c)	6/30 (20%)	8/31 (26%)	2/20 (10%)
Week of First Observation	87	70	85
Life Table Tests (d)	P=0.479	P=0.498	P=0.543
Incidental Tumor Tests (d)	P=0.334N	P=0.545	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.276N		
Fisher Exact Test (d)		P=0.583	P=0.322N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	17/49 (35%)	11/50 (22%)
Adjusted Rates (b)	32.0%	49.7%	49.2%
Terminal Rates (c)	9/32 (28%)	14/31 (45%)	9/20 (45%)
Week of First Observation	89	85	98
Life Table Tests (d)	P=0.122	P=0.108	P=0.171
Incidental Tumor Tests (d)	P=0.251	P=0.088	P=0.294
Cochran-Armitage Trend Test (d)	P=0.545		
Fisher Exact Test (d)		P=0.119	P=0.595N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	12/50 (24%)	17/49 (35%)	11/50 (22%)
Adjusted Rates (b)	33.5%	49.7%	49.2%
Terminal Rates (c)	9/32 (28%)	14/31 (45%)	9/20 (45%)
Week of First Observation	68	85	98
Life Table Tests (d)	P=0.184	P=0.159	P=0.249
Incidental Tumor Tests (d)	P=0.375	P=0.130	P=0.438
Cochran-Armitage Trend Test (d)	P=0.455N		
Fisher Exact Test (d)		P=0.172	P=0.500N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	3/48 (6%)	2/45 (4%)
Adjusted Rates (b)	5.4%	9.7%	8.3%
Terminal Rates (c)	1/32 (3%)	3/31 (10%)	1/19 (5%)
Week of First Observation	89	104	92
Life Table Tests (d)	P=0.414	P=0.477	P=0.554
Incidental Tumor Tests (d)	P=0.443	P=0.472	P=0.601
Cochran-Armitage Trend Test (d)	P=0.567		
Fisher Exact Test (d)		P=0.500	P=0.666

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	150 mg/kg	300 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/48 (19%)	6/48 (13%)	4/45 (9%)
Adjusted Rates (b)	25.4%	18.4%	14.8%
Terminal Rates (c)	6/32 (19%)	5/31 (16%)	2/19 (11%)
Week of First Observation	91	90	71
Life Table Tests (d)	P=0.258N	P=0.312N	P=0.325N
Incidental Tumor Tests (d)	P=0.109N	P=0.345N	P=0.116N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Test (d)		P=0.288N	P=0.142N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/48 (21%)	8/48 (17%)	6/45 (13%)
Adjusted Rates (b)	28.3%	24.7%	24.9%
Terminal Rates (c)	7/32 (22%)	7/31 (23%)	4/19 (21%)
Week of First Observation	91	90	71
Life Table Tests (d)	P=0.464N	P=0.425N	P=0.525N
Incidental Tumor Tests (d)	P=0.267N	P=0.461N	P=0.276N
Cochran-Armitage Trend Test (d)	P=0.205N		
Fisher Exact Test (d)		P=0.397N	P=0.248N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	3.1%	3.2%	15.7%
Terminal Rates (c)	1/32 (3%)	1/31 (3%)	2/20 (10%)
Week of First Observation	104	104	61
Life Table Tests (d)	P=0.047	P=0.755	P=0.093
Incidental Tumor Tests (d)	P=0.102	P=0.755	P=0.183
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.753	P=0.181
Preputial Gland: Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.7%	5.0%
Terminal Rates (c)	0/32 (0%)	3/31 (10%)	1/20 (5%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.240	P=0.115	P=0.406
Incidental Tumor Tests (d)	P=0.240	P=0.115	P=0.406
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.121	P=0.500
Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	0.0%	12.3%	8.5%
Terminal Rates (c)	0/32 (0%)	3/31 (10%)	1/20 (5%)
Week of First Observation		96	98
Life Table Tests (d)	P=0.121	P=0.061	P=0.167
Incidental Tumor Tests (d)	P=0.210	P=0.055	P=0.254
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.059	P=0.247
Testis: Interstitial Cell Tumor			
Overall Rates (a)	44/50 (88%)	41/50 (82%)	47/50 (94%)
Adjusted Rates (b)	95.7%	100.0%	100.0%
Terminal Rates (c)	30/32 (94%)	31/31 (100%)	20/20 (100%)
Week of First Observation	66	63	60
Life Table Tests (d)	P=0.002	P=0.479N	P=0.004
Incidental Tumor Tests (d)	P=0.104	P=0.651N	P=0.238
Cochran-Armitage Trend Test (d)	P=0.221		
Fisher Exact Test (d)		P=0.289N	P=0.243

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (*Continued*)

	Vehicle Control	150 mg/kg	300 mg/kg
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	3.1%	0.0%	15.9%
Terminal Rates (c)	1/32 (3%)	0/31 (0%)	2/20 (10%)
Week of First Observation	104		71
Life Table Tests (d)	P=0.041	P=0.506N	P=0.093
Incidental Tumor Tests (d)	P=0.097	P=0.506N	P=0.183
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor 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).

TABLE A4a. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	50	0	--
1,2-Dichlorobenzene	50	0	--
Benzene	50	1	Tubular cell adenocarcinoma
TOTAL	150	1 (0.7%)	
Overall Historical Incidence			
	1,098	1	Tubular cell adenoma
		2	Adenocarcinoma, NOS
		2	Tubular cell adenocarcinoma
TOTAL	Benign	1 (0.1%)	
	Malignant	4 (0.4%)	
	Combined	5 (0.5%)	

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No more than one tumor was observed in any vehicle control group.

TABLE A4b. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	8/50
1,2-Dichlorobenzene	10/50
Benzene	7/50
TOTAL	25/150 (16.7%)
SD (b)	3.06%
Range (c)	
High	10/50
Low	7/50
Overall Historical Incidence	
TOTAL	152/1,100 (13.8%)
SD (b)	8.12%
Range (c)	
High	14/50
Low	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are reported for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls (b)
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	3/50
1,2-Dichlorobenzene	3/50
Benzene	3/50
TOTAL	9/150 (6.0%)
SD (c)	0.00%
Range (d)	
High	3/50
Low	3/50
Overall Historical Incidence	
TOTAL	42/1,100 (3.8%)
SD (c)	2.95%
Range (d)	
High	6/50
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes mesothelioma, NOS, benign and malignant from all tissue sites combined
(c) Standard deviation
(d) Range and SD are reported for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Ulcer, chronic		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhagic cyst			1 (2%)
Inflammation, granulomatous focal	5 (10%)		
Necrosis, fat	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(48)	(47)	(45)
Inflammation, acute focal			1 (2%)
#Lung	(50)	(50)	(49)
Congestion, acute	2 (4%)	3 (6%)	
Edema, NOS	2 (4%)		
Hemorrhage		1 (2%)	1 (2%)
Inflammation, interstitial	5 (10%)	2 (4%)	4 (8%)
Pneumonia, aspiration		2 (4%)	2 (4%)
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse			1 (2%)
Inflammation, chronic focal	2 (4%)		
Granuloma, NOS	2 (4%)		
Perivascular cuffing	1 (2%)		
Foreign material, NOS	5 (10%)	12 (24%)	16 (33%)
Hyperplasia, alveolar epithelium	3 (6%)		2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(47)
Myelofibrosis		1 (2%)	
Hyperplasia, hematopoietic	2 (4%)		3 (6%)
Hyperplasia, reticulum cell	1 (2%)		
Hypoplasia, hematopoietic	2 (4%)		1 (2%)
#Splenic follicles	(49)	(48)	(49)
Depletion, lymphoid	2 (4%)		
#Splenic red pulp	(49)	(48)	(49)
Inflammation, granulomatous focal			1 (2%)
Fibrosis, focal	3 (6%)	2 (4%)	3 (6%)
Fibrosis, diffuse			1 (2%)
Hemosiderosis		1 (2%)	
Atrophy, fatty	1 (2%)		
Hematopoiesis	4 (8%)	1 (2%)	1 (2%)
#Mandibular lymph node	(44)	(48)	(39)
Plasmacytosis			1 (3%)
#Mediastinal lymph node	(44)	(48)	(39)
Pigmentation, NOS			1 (3%)
#Mesenteric lymph node	(44)	(48)	(39)
Edema, NOS			1 (3%)
#Lung	(50)	(50)	(49)
Leukocytosis, NOS	1 (2%)		
#Thymus	(42)	(36)	(39)
Hyperplasia, epithelial			2 (5%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(44)	(48)	(39)
Lymphangiectasis		1 (2%)	1 (3%)
#Heart	(50)	(50)	(49)
Thrombus, organized		1 (2%)	
Inflammation, acute focal			1 (2%)
#Heart/atrium	(50)	(50)	(49)
Thrombus, organized	2 (4%)		1 (2%)
Thrombus, fibrin	1 (2%)	1 (2%)	
#Myocardium	(50)	(50)	(49)
Inflammation, chronic focal	2 (4%)		
Fibrosis, focal	1 (2%)		
Degeneration, NOS	46 (92%)	47 (94%)	39 (80%)
#Endocardium	(50)	(50)	(49)
Fibrosis, multifocal		1 (2%)	
#Hepatic sinusoid	(50)	(49)	(50)
Dilatation, NOS	1 (2%)	3 (6%)	
#Pancreas	(50)	(48)	(46)
Periarteritis	2 (4%)	1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(49)	(45)
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	1 (2%)		
Atrophy, focal		1 (2%)	
#Liver	(50)	(49)	(50)
Inflammation, granulomatous focal			1 (2%)
Necrosis, focal	2 (4%)		
Basophilic cyto change	32 (64%)	23 (47%)	14 (28%)
Focal cellular change	8 (16%)	9 (18%)	7 (14%)
#Intrahepatic bile duct	(50)	(49)	(50)
Hyperplasia, NOS	1 (2%)		
#Liver/centrilobular	(50)	(49)	(50)
Congestion, passive			1 (2%)
Necrosis, focal	1 (2%)		
Hemosiderosis			1 (2%)
#Liver/periportal	(50)	(49)	(50)
Cytoplasmic vacuolization			1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)
Degeneration, cystic	1 (2%)	5 (10%)	2 (4%)
Cytoplasmic vacuolization		1 (2%)	1 (2%)
Hyperplasia, focal		1 (2%)	
#Pancreas	(50)	(48)	(46)
Necrosis, fat	1 (2%)		
#Pancreatic acinus	(50)	(48)	(46)
Focal cellular change		2 (4%)	3 (7%)
Atrophy, focal	14 (28%)	9 (19%)	12 (26%)
Atrophy, diffuse	1 (2%)		1 (2%)
Hyperplasia, focal	8 (16%)	6 (13%)	8 (17%)
#Esophagus	(50)	(50)	(49)
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute/chronic			1 (2%)
#Gastric mucosa	(49)	(47)	(45)
Mineralization			1 (2%)
Inflammation, acute focal			1 (2%)
#Glandular stomach	(49)	(47)	(45)
Ulcer, acute		1 (2%)	1 (2%)
Necrosis, focal			2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(49)	(47)	(45)
Hemorrhage		1 (2%)	
Ulcer, acute			3 (7%)
Ulcer, chronic	1 (2%)		
Ulcer, perforated		1 (2%)	1 (2%)
Hyperplasia, epithelial		1 (2%)	2 (4%)
Hyperkeratosis			2 (4%)
#Duodenum	(48)	(45)	(44)
Inflammation, acute necrotizing			1 (2%)
#Colon	(47)	(45)	(43)
Ulcer, acute		1 (2%)	
Parasitism		3 (7%)	2 (5%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, NOS			1 (2%)
Pyelonephritis, acute	1 (2%)	1 (2%)	
Pyelonephritis, chronic			1 (2%)
Nephropathy	42 (84%)	42 (84%)	46 (92%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS			4 (8%)
Multiple cysts		1 (2%)	3 (6%)
Pigmentation, NOS			1 (2%)
Cytoplasmic aggregate, NOS		1 (2%)	
#Kidney/medulla	(50)	(50)	(50)
Mineralization	4 (8%)	46 (92%)	47 (94%)
#Kidney/tubule	(50)	(50)	(50)
Mineralization	2 (4%)		
Necrosis, focal		1 (2%)	
Necrosis, diffuse	1 (2%)		
Pigmentation, NOS	1 (2%		
Hyperplasia, focal		1 (2%)	9 (18%)
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, acute diffuse		1 (2%)	
Hyperplasia, epithelial	1 (2%)	30 (60%)	31 (62%)
#Urinary bladder	(48)	(45)	(43)
Hemorrhage		1 (2%)	
Inflammation, acute focal		1 (2%)	1 (2%)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute necrotizing			1 (2%)
Necrosis, diffuse	1 (2%)		
Necrosis, hemorrhagic			1 (2%)
Polyp, inflammatory	1 (2%)		
Metaplasia, squamous			1 (2%)
*Prostatic urethra	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(45)	(49)	(49)
Degeneration, NOS			1 (2%)
Focal cellular change			1 (2%)
Cytomegaly	2 (4%)		
Hyperplasia, focal	13 (29%)	3 (6%)	7 (14%)
Angiectasis			3 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Pituitary posterior	(45)	(49)	(49)
Gliosis			1 (2%)
Hyperplasia, epithelial	1 (2%)		1 (2%)
#Adrenal cortex	(50)	(49)	(50)
Inflammation, acute necrotizing			1 (2%)
Degeneration, lipoid	5 (10%)	3 (6%)	5 (10%)
Cytoplasmic vacuolization	1 (2%)		1 (2%)
Focal cellular change	3 (6%)		
Hyperplasia, focal	14 (28%)	10 (20%)	23 (46%)
Angiectasis		1 (2%)	
#Adrenal medulla	(50)	(49)	(50)
Hyperplasia, focal	13 (26%)	13 (27%)	17 (34%)
#Thyroid	(48)	(48)	(45)
Follicular cyst, NOS	5 (10%)	4 (8%)	4 (9%)
Hyperplasia, C-cell	13 (27%)	8 (17%)	14 (31%)
Hyperplasia, follicular cell	2 (4%)	1 (2%)	1 (2%)
#Thyroid follicle	(48)	(48)	(45)
Multiple cysts			2 (4%)
#Parathyroid	(42)	(42)	(38)
Hyperplasia, NOS	4 (10%)	13 (31%)	20 (53%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS	3 (6%)		
Hyperplasia, cystic	1 (2%)	5 (10%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	2 (4%)	1 (2%)	2 (4%)
Inflammation, active chronic	2 (4%)		1 (2%)
Inflammation, pyogranulomatous			1 (2%)
Hyperplasia, diffuse			1 (2%)
#Prostate	(49)	(49)	(48)
Multiple cysts			1 (2%)
Inflammation, suppurative	1 (2%)		
Inflammation, acute diffuse		1 (2%)	
Inflammation, acute hemorrhagic			1 (2%)
Inflammation, pyogranulomatous		1 (2%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		
#Periprostatic tissue	(49)	(49)	(48)
Inflammation, granulomatous focal			1 (2%)
#Testis	(50)	(50)	(50)
Atrophy, NOS	2 (4%)	1 (2%)	
Atrophy, diffuse	5 (10%)	1 (2%)	2 (4%)
Hyperplasia, interstitial cell	30 (60%)	35 (70%)	39 (78%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
NERVOUS SYSTEM			
#Brain	(49)	(48)	(48)
Necrosis, hemorrhagic	1 (2%)	2 (4%)	1 (2%)
#Hypothalamus	(49)	(48)	(48)
Hemorrhage	1 (2%)		
Atrophy, pressure	1 (2%)	1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye/anterior chamber	(50)	(50)	(50)
Inflammation, acute hemorrhagic			1 (2%)
*Eye/cornea	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, diffuse	2 (4%)	5 (10%)	4 (8%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)	5 (10%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
*Cortex of bone	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		1 (2%)
Hyperplasia, diffuse			1 (2%)
*Cervical vertebra other	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation with fibrosis			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous focal	1 (2%)	1 (2%)	1 (2%)
Necrosis, fat	2 (4%)	3 (6%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)	2 (4%)	1 (2%)
Fibrosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)
Cortical carcinoma, metastatic			1 (2%)
C-cell carcinoma, metastatic	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	15 (30%)	10 (20%)	8 (16%)
#Spleen	(50)	(50)	(49)
Sarcoma, NOS		1 (2%)	
Leukemia, mononuclear cell			1 (2%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Intestinal tract	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)		
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	1 (2%)	2 (4%)
#Pancreas	(50)	(50)	(49)
Acinar cell adenoma			1 (2%)
URINARY SYSTEM			
#Urinary bladder	(49)	(49)	(46)
Adenocarcinoma, NOS, metastatic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(49)	(49)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	15 (31%)	13 (27%)	11 (22%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma	3 (6%)	1 (2%)	2 (4%)
Cortical carcinoma			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	7 (14%)	5 (10%)	2 (4%)
Pheochromocytoma, malignant	1 (2%)		
Ganglioneuroma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(50)	(48)
Follicular cell adenoma		2 (4%)	1 (2%)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	9 (18%)	13 (26%)	5 (10%)
C-cell carcinoma	5 (10%)	3 (6%)	2 (4%)
#Parathyroid	(40)	(38)	(42)
Adenoma, NOS	1 (3%)	1 (3%)	
#Pancreatic islets	(50)	(50)	(49)
Islet cell adenoma		4 (8%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS		1 (2%)	1 (2%)
Fibroadenoma	12 (24%)	12 (24%)	5 (10%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	2 (4%)	
Adenocarcinoma, NOS		2 (4%)	
*Vagina	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)	
#Uterus	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	2 (4%)
Adenocarcinoma, NOS, metastatic			1 (2%)
Leiomyosarcoma		1 (2%)	
Endometrial stromal polyp	9 (18%)	10 (20%)	7 (14%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		
Astrocytoma	1 (2%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Ear	(50)	(50)	(50)
Neurofibrosarcoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
C-cell carcinoma, metastatic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Leiomyosarcoma	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Tail			
Fibrosarcoma	1		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	3	9
Moribund sacrifice	11	7	9
Terminal sacrifice	35	39	29
Dosing accident		1	3
TUMOR SUMMARY			
Total animals with primary tumors**	43	45	36
Total primary tumors	87	93	60
Total animals with benign tumors	37	41	28
Total benign tumors	60	68	37
Total animals with malignant tumors	20	21	17
Total malignant tumors	26	24	21
Total animals with secondary tumors##	2	2	2
Total secondary tumors	3	2	4
Total animals with tumors uncertain--benign or malignant	1	1	2
Total uncertain tumors	1	1	2

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: VEHICLE CONTROL

ANIMAL NUMBER	017	044	023	002	007	012	050	035	016	038	006	029	036	025	045	001	003	004	005	008	009	110	111	113	114
WEEKS ON STUDY	034	067	077	086	087	087	089	095	098	098	101	101	101	102	102	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																						X			
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS													X												
Adenoma, NOS			X				X							X	X							X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma															X										X
Pheochromocytoma					X			X		X						X				X				X	
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma										X							X					X			X
C-cell carcinoma						X		X				X							X						
Parathyroid	−	+	+	+	−	+	−	−	+	+	−	−	+	−	+	+	+	+	+	+	−	+	+	+	+
Adenoma, NOS		X																							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	+	+
Fibroadenoma														X			X					X			X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp											X				X	X			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive													X												
Astrocytoma		X																							
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Neurofibrosarcoma																				X					
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
C-cell carcinoma, metastatic								X																	
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell				X	X	X		X	X	X							X		X	X	X				
Tail																									
Fibrosarcoma										X															

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0151	0181	0191	0200	0211	0222	0244	0266	0277	0288	0300	0311	0322	0333	0344	0377	0399	0400	0411	0422	0433	0466	0477	0488	0499	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Fibroma													X													1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																	X									2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule									X																	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS		X				X		X			X	X				X		X		X	X		X			15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																X										3
Pheochromocytoma	X																									7
Pheochromocytoma, malignant															X											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell adenoma			X					X			X				X								X			9
C cell carcinoma																	X									5
Parathyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	40
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma		X			X				X				X	X			X					X	X			12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp			X			X		X						X	X											9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurofibrosarcoma																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
C cell carcinoma, metastatic																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell									X			X	X						X					X		15
Tail																										
Fibrosarcoma																										1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: LOW DOSE

ANIMAL NUMBER	0028	0022	0031	0005	0007	0026	0036	0048	0155	0042	0039	0001	0002	0003	0004	0006	0008	0009	0110	0111	0112	0113	0114	0116	0117
WEEKS ON STUDY	0667	0669	0775	0882	0888	0991	0991	0995	0998	0999	1000	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X													
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X							X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Trachea	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS			X							X	X	X							X		X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma	X				X	X																X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma				X											X										
Follicular cell carcinoma																									
C-cell adenoma						X												X	X				X		
C-cell carcinoma																									
Parathyroid	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma									X					X					X					X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																					X				X
Adenocarcinoma, NOS					X																				
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Leiomyosarcoma																X									
Endometrial stromal polyp												X	X	X								X		X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma	X																								
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic										X															
Leukemia, mononuclear cell				X			X	X							X										X

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

ANIMAL NUMBER	0018	0019	0020	0021	0023	0024	0025	0027	0029	0030	0032	0033	0034	0035	0037	0038	0040	0041	0043	0044	0045	0046	0047	0049	0050	TOTAL:
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	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Keratoacanthoma																				X						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS											X															1
Adenoma, NOS													X	X			X		X		X					13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma															X											1
Pheochromocytoma																				X						5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
Follicular cell carcinoma					X																					1
C-cell adenoma				X		X	X						X		X	X	X			X					X	13
C-cell carcinoma	X													X								X				3
Parathyroid	+	−	+	−	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	38
Adenoma, NOS																		X								1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma				X								X									X					4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	N	N	+	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	*50
Adenoma, NOS											X															1
Adenocarcinoma, NOS																	X									1
Fibroadenoma	X			X						X				X		X	X					X		X		12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
Adenocarcinoma, NOS																								X		2
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Leiomyosarcoma																										1
Endometrial stromal polyp		X			X				X	X														X		10
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leiomyosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
Leukemia, mononuclear cell	X	X			X															X				X		10

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: HIGH DOSE

ANIMAL NUMBER	0 1 4	0 0 7	0 4 3	0 5 0	0 3 3	0 0 6	0 2 0	0 2 2	0 0 8	0 3 2	0 3 9	0 1 7	0 3 7	0 4 7	0 0 2	0 4 1	0 4 5	0 4 9	0 0 5	0 2 9	0 3 6	0 0 1	0 0 3	0 0 4	0 0 9
WEEKS ON STUDY	0 1 1	0 2 1	0 2 2	0 5 5	0 5 8	0 6 4	0 7 2	0 7 2	0 7 7	0 8 2	0 8 5	0 8 8	0 9 1	0 9 3	0 9 4	0 9 5	1 0 0	1 0 1	1 0 2	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Alveolar/bronchiolar carcinoma																									
Cortical carcinoma, metastatic																				X					
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																							X		
Lymph nodes	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma																									
Esophagus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	–	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic									X																
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X					X	X	X				X		
Adrenal	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																				X					
Pheochromocytoma															X										
Ganglioneuroma																									
Thyroid	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C cell adenoma												X													
C cell carcinoma																									
Parathyroid	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	N	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS														X											
Fibroadenoma																		X	X		X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenocarcinoma, NOS, metastatic									X																
Endometrial stromal polyp										X		X			X	X				X					
Ovary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																				X					
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																	X								
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell					X					X		X	X	X	X		X								
Intestinal tract																									
Adenocarcinoma, NOS									X																

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

ANIMAL NUMBER	0110	0111	0112	0113	0115	0116	0118	0119	0121	0123	0124	0125	0126	0127	0128	0130	0131	0134	0135	0138	0140	0142	0144	0146	0148	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X																								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																X										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Alveolar/bronchiolar carcinoma																									X	1
Cortical carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule															X											2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma	X																									1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	46
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenocarcinoma, NOS, metastatic																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS				X			X					X	X							X				X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma											X											X				2
Cortical carcinoma																										1
Pheochromocytoma																		X								2
Ganglioneuroma										X																1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma							X																			1
C cell adenoma					X					X								X	X							5
C cell carcinoma																						X		X		2
Parathyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	N	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma																			X		X					5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS							X			X																2
Adenocarcinoma, NOS, metastatic																										1
Endometrial stromal polyp																X	X									7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																						X				8
Intestinal tract																										
Adenocarcinoma, NOS																										1

*Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/50 (30%)	10/50 (20%)	9/50 (18%)
Adjusted Rates (b)	35.3%	23.3%	22.6%
Terminal Rates (c)	9/35 (26%)	7/39 (18%)	2/29 (7%)
Week of First Observation	86	82	58
Life Table Tests (d)	P=0.206N	P=0.147N	P=0.266N
Incidental Tumor Tests (d)	P=0.112N	P=0.199N	P=0.129N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.178N	P=0.121N
Pituitary Gland: Adenoma			
Overall Rates (a)	15/48 (31%)	13/49 (27%)	11/49 (22%)
Adjusted Rates (b)	38.8%	30.7%	32.6%
Terminal Rates (c)	11/34 (32%)	10/39 (26%)	7/29 (24%)
Week of First Observation	77	75	88
Life Table Tests (d)	P=0.359N	P=0.297N	P=0.414N
Incidental Tumor Tests (d)	P=0.232N	P=0.382N	P=0.297N
Cochran-Armitage Trend Test (d)	P=0.194N		
Fisher Exact Test (d)		P=0.386N	P=0.227N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	16/48 (33%)	14/49 (29%)	11/49 (22%)
Adjusted Rates (b)	40.3%	33.1%	32.6%
Terminal Rates (c)	11/34 (32%)	11/39 (28%)	7/29 (24%)
Week of First Observation	77	75	88
Life Table Tests (d)	P=0.291N	P=0.298N	P=0.342N
Incidental Tumor Tests (d)	P=0.170N	P=0.401N	P=0.220N
Cochran-Armitage Trend Test (d)	P=0.140N		
Fisher Exact Test (d)		P=0.387N	P=0.166N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	8.3%	2.6%	6.9%
Terminal Rates (c)	2/35 (6%)	1/39 (3%)	2/29 (7%)
Week of First Observation	102	104	104
Life Table Tests (d)	P=0.466N	P=0.274N	P=0.581N
Incidental Tumor Tests (d)	P=0.457N	P=0.335N	P=0.568N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.309N	P=0.510N
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	8.3%	2.6%	9.8%
Terminal Rates (c)	2/35 (6%)	1/39 (3%)	2/29 (7%)
Week of First Observation	102	104	102
Life Table Tests (d)	P=0.523	P=0.274N	P=0.579
Incidental Tumor Tests (d)	P=0.539	P=0.335N	P=0.604
Cochran-Armitage Trend Test (d)	P=0.585		
Fisher Exact Test (d)		P=0.309N	P=0.651
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	7/50 (14%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	17.4%	11.1%	6.1%
Terminal Rates (c)	4/35 (11%)	2/39 (5%)	1/29 (3%)
Week of First Observation	87	67	94
Life Table Tests (d)	P=0.101N	P=0.343N	P=0.141N
Incidental Tumor Tests (d)	P=0.066N	P=0.395N	P=0.109N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.380N	P=0.085N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	20.0%	11.1%	6.1%
Terminal Rates (c)	5/35 (14%)	2/39 (5%)	1/29 (3%)
Week of First Observation	87	67	94
Life Table Tests (d)	P=0.061N	P=0.245N	P=0.093N
Incidental Tumor Tests (d)	P=0.038N	P=0.283N	P=0.070N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.277N	P=0.049N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	0.0%	7.1%	3.4%
Terminal Rates (c)	0/35 (0%)	2/39 (5%)	1/29 (3%)
Week of First Observation		82	104
Life Table Tests (d)	P=0.324	P=0.136	P=0.462
Incidental Tumor Tests (d)	P=0.354	P=0.154	P=0.462
Cochran-Armitage Trend Test (d)	P=0.371		
Fisher Exact Test (d)		P=0.125	P=0.495
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/49 (18%)	13/50 (26%)	5/48 (10%)
Adjusted Rates (b)	24.7%	32.3%	16.0%
Terminal Rates (c)	8/35 (23%)	12/39 (31%)	4/29 (14%)
Week of First Observation	98	91	88
Life Table Tests (d)	P=0.297N	P=0.322	P=0.309N
Incidental Tumor Tests (d)	P=0.266N	P=0.302	P=0.278N
Cochran-Armitage Trend Test (d)	P=0.192N		
Fisher Exact Test (d)		P=0.251	P=0.205N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	5/49 (10%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	12.2%	7.7%	6.9%
Terminal Rates (c)	2/35 (6%)	3/39 (8%)	2/29 (7%)
Week of First Observation	87	104	104
Life Table Tests (d)	P=0.217N	P=0.324N	P=0.301N
Incidental Tumor Tests (d)	P=0.191N	P=0.391N	P=0.246N
Cochran-Armitage Trend Test (d)	P=0.163N		
Fisher Exact Test (d)		P=0.346N	P=0.227N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	14/49 (29%)	16/50 (32%)	7/48 (15%)
Adjusted Rates (b)	35.1%	39.8%	22.7%
Terminal Rates (c)	10/35 (29%)	15/39 (38%)	6/29 (21%)
Week of First Observation	87	91	88
Life Table Tests (d)	P=0.147N	P=0.532	P=0.162N
Incidental Tumor Tests (d)	P=0.115N	P=0.468	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.072N		
Fisher Exact Test (d)		P=0.440	P=0.077N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	0.0%	9.7%	0.0%
Terminal Rates (c)	0/35 (0%)	3/39 (8%)	0/29 (0%)
Week of First Observation		88	
Life Table Tests (d)	P=0.572	P=0.077	(e)
Incidental Tumor Tests (d)	P=0.582	P=0.076	(e)
Cochran-Armitage Trend Test (d)	P=0.616		
Fisher Exact Test (d)		P=0.059	(e)

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	12/50 (24%)	12/50 (24%)	5/50 (10%)
Adjusted Rates (b)	33.3%	29.9%	15.4%
Terminal Rates (c)	11/35 (31%)	11/39 (28%)	2/29 (7%)
Week of First Observation	102	98	101
Life Table Tests (d)	P=0.103N	P=0.480N	P=0.119N
Incidental Tumor Tests (d)	P=0.091N	P=0.546N	P=0.098N
Cochran-Armitage Trend Test (d)	P=0.050N		
Fisher Exact Test (d)		P=0.592	P=0.054N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	12/50 (24%)	13/50 (26%)	5/50 (10%)
Adjusted Rates (b)	33.3%	32.4%	15.4%
Terminal Rates (c)	11/35 (31%)	12/39 (31%)	2/29 (7%)
Week of First Observation	102	98	101
Life Table Tests (d)	P=0.109N	P=0.568N	P=0.119N
Incidental Tumor Tests (d)	P=0.096N	P=0.555	P=0.098N
Cochran-Armitage Trend Test (d)	P=0.052N		
Fisher Exact Test (d)		P=0.500	P=0.054N
Clitoral Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	2.5%	9.7%	0.0%
Terminal Rates (c)	0/35 (0%)	3/39 (8%)	0/29 (0%)
Week of First Observation	101	88	
Life Table Tests (d)	P=0.449N	P=0.205	P=0.538N
Incidental Tumor Tests (d)	P=0.429N	P=0.161	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.181	P=0.500N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	7/50 (14%)
Adjusted Rates (b)	24.1%	25.6%	19.0%
Terminal Rates (c)	7/35 (20%)	10/39 (26%)	2/29 (7%)
Week of First Observation	101	104	82
Life Table Tests (d)	P=0.497N	P=0.594	P=0.542N
Incidental Tumor Tests (d)	P=0.458N	P=0.526	P=0.483N
Cochran-Armitage Trend Test (d)	P=0.346N		
Fisher Exact Test (d)		P=0.500	P=0.393N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 600 mg/kg and vehicle control groups.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Hyperplasia, basal cell	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, active chronic	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Congestion, acute	2 (4%)		3 (6%)
Inflammation, interstitial	1 (2%)	1 (2%)	
Pneumonia, aspiration	4 (8%)	2 (4%)	2 (4%)
Inflammation, acute/chronic	1 (2%)		
Granuloma, NOS	1 (2%)	1 (2%)	
Parasitism			1 (2%)
Foreign material, NOS	9 (18%)	14 (28%)	6 (12%)
Metaplasia, osseous	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Blood	(50)	(50)	(50)
Leukocytosis, neutrophilic	1 (2%)		
#Bone marrow	(50)	(50)	(49)
Myelofibrosis			2 (4%)
Hyperplasia, hematopoietic		2 (4%)	2 (4%)
Hyperplasia, reticulum cell	2 (4%)		
Hypoplasia, hematopoietic	1 (2%)	2 (4%)	3 (6%)
#Splenic follicles	(50)	(50)	(49)
Depletion, lymphoid	1 (2%)		1 (2%)
#Splenic red pulp	(50)	(50)	(49)
Congestion, acute			1 (2%)
Fibrosis, focal		1 (2%)	1 (2%)
Hematopoiesis	4 (8%)	5 (10%)	3 (6%)
#Mandibular lymph node	(50)	(50)	(46)
Plasmacytosis	1 (2%)		
#Cervical lymph node	(50)	(50)	(46)
Abscess, chronic		1 (2%)	
#Lung	(50)	(50)	(50)
Leukemoid reaction		1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Leukemoid reaction		1 (2%)	
#Thymus	(46)	(43)	(42)
Hyperplasia, epithelial	1 (2%)		
CIRCULATORY SYSTEM			
#Inguinal lymph node	(50)	(50)	(46)
Lymphangiectasis	1 (2%)		
#Myocardium	(50)	(50)	(50)
Mineralization	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	3 (6%)
Degeneration, NOS	43 (86%)	43 (86%)	39 (78%)
*Aorta	(50)	(50)	(50)
Mineralization			1 (2%)
#Hepatic sinusoid	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	3 (6%)	1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Acanthosis		1 (2%)	
#Salivary gland	(50)	(50)	(50)
Focal cellular change		1 (2%)	
#Liver	(50)	(50)	(50)
Granuloma, NOS	4 (8%)	1 (2%)	
Degeneration, lipoid	1 (2%)		
Necrosis, focal	1 (2%)		
Basophilic cyto change	37 (74%)	37 (74%)	17 (34%)
Focal cellular change	4 (8%)	1 (2%)	
Eosinophilic cyto change		1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, diffuse		3 (6%)	1 (2%)
Hepatocytomegaly			1 (2%)
#Liver/periportal	(50)	(50)	(50)
Cytoplasmic vacuolization	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(50)
Degeneration, cystic		1 (2%)	
#Pancreas	(50)	(50)	(49)
Accessory structure	1 (2%)		
#Pancreatic acinus	(50)	(50)	(49)
Focal cellular change	3 (6%)		3 (6%)
Atrophy, focal	5 (10%)	10 (20%)	6 (12%)
Hyperplasia, focal	5 (10%)	3 (6%)	
#Periesophageal tissue	(50)	(50)	(49)
Inflammation, acute focal			1 (2%)
#Stomach	(50)	(50)	(46)
Cyst, NOS	1 (2%)		
#Glandular stomach	(50)	(50)	(46)
Ulcer, acute	1 (2%)		
Necrosis, focal	4 (8%)	3 (6%)	2 (4%)
Hyperplasia, focal			1 (2%)
#Forestomach	(50)	(50)	(46)
Ulcer, acute	1 (2%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)		
Hyperkeratosis		3 (6%)	
Acanthosis		3 (6%)	
#Colon	(49)	(48)	(47)
Cyst, NOS	1 (2%)		
Parasitism	1 (2%)	1(2%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(49)
Hydronephrosis		1 (2%)	2 (4%)
Multiple cysts	1 (2%)		
Inflammation, acute necrotizing			1 (2%)
Nephropathy	21 (43%)	32 (64%)	41 (84%)
Infarct, focal		5 (10%)	3 (6%)
Pigmentation, NOS	1 (2%)		
#Kidney/cortex	(49)	(50)	(49)
Cyst, NOS		1 (2%)	1 (2%)
#Kidney/medulla	(49)	(50)	(49)
Mineralization	5 (10%)	1 (2%)	10 (20%)
#Renal papilla	(49)	(50)	(49)
Necrosis, NOS			1 (2%)
#Kidney/pelvis	(49)	(50)	(49)
Mineralization			1 (2%)
Hyperplasia, epithelial			2 (4%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder	(49)	(49)	(46)
Calculus, gross observation only			1 (2%)
Necrosis, hemorrhagic			1 (2%)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(49)	(49)
Cyst, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Degeneration, NOS	1 (2%)		
Degeneration, lipoid	1 (2%)		
Hyperplasia, focal	12 (25%)	19 (39%)	7 (14%)
#Adrenal cortex	(50)	(50)	(49)
Degeneration, lipoid	7 (14%)	3 (6%)	5 (10%)
Focal cellular change	3 (6%)	4 (8%)	
Hyperplasia, focal	23 (46%)	25 (50%)	14 (29%)
Angiectasis			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	9 (18%)	12 (24%)	6 (12%)
#Thyroid	(49)	(50)	(48)
Follicular cyst, NOS			4 (8%)
Hyperplasia, C-cell	28 (57%)	22 (44%)	28 (58%)
#Thyroid follicle	(49)	(50)	(48)
Multiple cysts		3 (6%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	29 (58%)	37 (74%)	30 (60%)
#Uterus	(50)	(50)	(50)
Dilatation, NOS	5 (10%)	9 (18%)	5 (10%)
Hemorrhage			2 (4%)
Inflammation, acute diffuse		1 (2%)	
Metaplasia, squamous			1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		
Hyperplasia, epithelial	1 (2%)	2 (4%)	5 (10%)
#Endometrial gland	(50)	(50)	(50)
Cyst, NOS	3 (6%)	1 (2%)	3 (6%)
Multiple cysts	5 (10%)	9 (18%)	5 (10%)
#Ovary	(50)	(50)	(49)
Follicular cyst, NOS	5 (10%)	8 (16%)	3 (6%)
Parovarian cyst	3 (6%)	2 (4%)	1 (2%)
Atrophy, NOS	2 (4%)		
#Ovary/follicle	(50)	(50)	(49)
Multiple cysts	1 (2%)	1 (2%)	2 (4%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Necrosis, focal	1 (2%)		
Necrosis, hemorrhagic	1 (2%)	1 (2%)	
#Hypothalamus	(50)	(50)	(50)
Atrophy, pressure	4 (8%)	8 (16%)	4 (8%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye/retina	(50)	(50)	(50)
Atrophy, diffuse	4 (8%)	2 (4%)	5 (10%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	3 (6%)	2 (4%)	4 (8%)
MUSCULOSKELETAL SYSTEM			
*Cortex of bone	(50)	(50)	(50)
Hyperplasia, diffuse	5 (10%)	3 (6%)	2 (4%)
*Phalanges of foot	(50)	(50)	(50)
Osteoarthritis	1 (2%)		
Hyperostosis	1 (2%)		
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Granuloma, foreign body			2 (4%)
*Mediastinum	(50)	(50)	(50)
Granuloma, foreign body	1 (2%)		
*Mesentery	(50)	(50)	(50)
Necrosis, fat	4 (8%)	5 (10%)	6 (12%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
Neurofibroma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	1 (2%)		1 (2%)
Fibrosarcoma	†9 (18%)	2 (4%)	3 (6%)
Neurofibrosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	4 (8%)	3 (6%)	2 (4%)
Alveolar/bronchiolar adenoma	6 (12%)	8 (16%)	2 (4%)
Alveolar/bronchiolar carcinoma		5 (10%)	
Sarcoma, NOS, metastatic			1 (2%)
Fibrosarcoma, metastatic	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	
Malignant lymphoma, mixed type	7 (14%)	7 (14%)	6 (12%)
#Spleen	(47)	(48)	(46)
Malignant lymphoma, mixed type	1 (2%)		
#Jejunum	(44)	(43)	(44)
Malignant lymphoma, lymphocytic type			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Bone marrow	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)		
#Spleen	(47)	(48)	(46)
Hemangiosarcoma	1 (2%)		3 (7%)
#Splenic red pulp	(47)	(48)	(46)
Hemangiosarcoma		2 (4%)	
#Liver	(50)	(49)	(50)
Hemangiosarcoma	3 (6%)	2 (4%)	
Hemangiosarcoma, unclear primary or metastatic		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Hepatocellular adenoma	5 (10%)	13 (27%)	16 (32%)
Hepatocellular carcinoma	14 (28%)	11 (22%)	32 (64%)
Hepatoblastoma			4 (8%)
Neurofibrosarcoma, metastatic			1 (2%)
#Gastric fundal gland	(45)	(46)	(44)
Adenocarcinoma, NOS			1 (2%)
#Forestomach	(45)	(46)	(44)
Squamous cell papilloma			1 (2%)
URINARY SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal	(47)	(48)	(49)
Cortical adenoma		1 (2%)	1 (2%)
#Adrenal/capsule	(47)	(48)	(49)
Adenoma, NOS		3 (6%)	
#Adrenal medulla	(47)	(48)	(49)
Pheochromocytoma		2 (4%)	3 (6%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(47)	(48)	(47)
Follicular cell adenoma	1 (2%)	1 (2%)	3 (6%)
Follicular cell carcinoma		1 (2%)	
#Thyroid follicle	(47)	(48)	(47)
Papillary adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
#Testis	(50)	(50)	(48)
Interstitial cell tumor			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Intercostal muscle	(50)	(50)	(50)
Sarcoma, NOS, metastatic			1 (2%)
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma, unclear primary or metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	5	6
Moribund sacrifice	10	5	5
Terminal sacrifice	28	32	30
Dosing accident	1	8	1
Accidentally killed, NOS	2		8

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	35	33	42
Total primary tumors	56	62	84
Total animals with benign tumors	16	20	24
Total benign tumors	16	30	30
Total animals with malignant tumors	30	22	36
Total malignant tumors	39	31	53
Total animals with secondary tumors##	6	3	6
Total secondary tumors	6	3	7
Total animals with tumors uncertain--benign or malignant	1		
Total uncertain tumors	1		
Total animals with tumors uncertain--primary or metastatic		1	1
Total uncertain tumors		1	1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ
† Multiple occurrence of morphology in the same organ. Tissue is counted once only.

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: VEHICLE CONTROL

ANIMAL NUMBER	0023	0032	0033	0001	0006	0029	0009	0025	0026	0019	0008	0024	0049	0039	0045	0016	0038	0002	0047	0048	0050	0043	0003	0004	0005
WEEKS ON STUDY	011	011	011	038	059	067	074	085	085	088	089	090	090	093	094	097	097	098	098	099	099	102	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																				X					
Fibrosarcoma					X			X				X					X					X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X	X		X												
Alveolar/bronchiolar adenoma										X	X										X				
Fibrosarcoma, metastatic																	X					X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	−	−	−	+	−	+	+	−	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X				X													X
Hepatocellular carcinoma							X		X	X	X		X	X							X				
Hemangiosarcoma																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	N	N	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	−	−	−	+	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Thyroid	−	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	+	−	−	+	−	−	+	−	+	+	+	−	−	−	+	−	−	−	+	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																				X					
Malignant lymphoma, histiocytic type															X										
Malignant lymphoma, mixed type									X									X	X						

+ Tissue examined microscopically
−. Required tissue not examined microscopically
X Tumor incidence
N. Necropsy, no autolysis, no microscopic examination
S· Animal missexed
@· Multiple occurrence of morphology

No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M. Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0007	0101	0111	0112	0113	0114	0115	0117	0118	0120	0121	0122	0127	0128	0130	0131	0134	0135	0136	0137	0140	0141	0142	0144	0146	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma													X						X@	X	X					9
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic										X																4
Alveolar/bronchiolar adenoma	X					X														X						6
Fibrosarcoma, metastatic																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma						X																				1
Malignant lymphoma, mixed type										X																1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	–	–	+	–	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X			X								5
Hepatocellular carcinoma					X		X	X		X				X	X			X								14
Hemangiosarcoma								X										X								3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	41
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																							X			1
Parathyroid	+	+	+	–	+	–	+	+	+	+	+	+	–	–	–	–	–	+	–	–	+	–	+	–	–	24
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																			X							2
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type						X							X	X		X										7

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: LOW DOSE

ANIMAL NUMBER	041	029	005	025	026	031	037	047	019	010	015	039	045	036	040	044	020	049	001	002	003	004	006	007	008
WEEKS ON STUDY	008	010	111	111	111	111	111	111	226	034	800	900	900	902	903	908	101	103	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Neurofibroma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X					X							
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																		X			X				
Trachea	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	−	+	−	−	+	−	−	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	+	+	+	−	−	−	+	−	−	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X			X	X	X		
Hepatocellular carcinoma											X	X	X	X		X		X				X			X
Hemangiosarcoma																X									
Hemangiosarcoma, unc prim or met																									
Bile duct	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	N	+	+	N	N	+	N	N	+	N	+	N	N	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	−	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	−	−	+	−	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	−	+	−	+	−	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X				
Cortical adenoma																			X						
Pheochromocytoma																		X							
Thyroid	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																X									
Follicular cell carcinoma																									
Parathyroid	+	−	−	−	+	−	+	−	−	−	+	+	−	+	−	−	−	+	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																	X				X				X

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

ANIMAL NUMBER	0009	0011	0012	0013	0014	0016	0017	0018	0021	0022	0023	0024	0027	0028	0030	0032	0033	0034	0035	0038	0042	0043	0046	0048	0050	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma					X																					1
Neurofibroma								X																		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma															X											2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																			X							3
Alveolar/bronchiolar adenoma					X	X				X			X					X		X		X			8
Alveolar/bronchiolar carcinoma								X				X				X										5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																					X	X				2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	41
Thymus	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X				X			X	X	X			X					X					X	X		13
Hepatocellular carcinoma																X			X	X						11
Hemangiosarcoma																							X			2
Hemangiosarcoma, unc prim or meta																						X				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS						X								X												3
Cortical adenoma																										1
Pheochromocytoma																			X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Follicular cell carcinoma								X																		1
Parathyroid	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type		X					X	X								X										7

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: HIGH DOSE

ANIMAL NUMBER	009	014	017	027	043	046	048	038	006	024	031	026	013	015	033	041	011	035	016	001	002	003	004	005	007
WEEKS ON STUDY	011	011	011	011	011	011	011	012	084	086	088	089	090	090	091	091	093	095	097	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Fibroma																									
Fibrosarcoma													X	X						X					
Neurofibrosarcoma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic											X														
Alveolar/bronchiolar adenoma																									
Sarcoma, NOS, metastatic																	X								
Fibrosarcoma, metastatic														X											
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+
Hemangiosarcoma															X									X	
Lymph nodes	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Thymus	+	+	+	−	−	−	+	+	−	−	−	+	+	+	+	−	−	−	+	+	+	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																					X				
Hepatocellular adenoma											X		X			X				X					X
Hepatocellular carcinoma									X	X	X	X			X	X		X	X		X	X	X	X	X
Hepatoblastoma											X														
Neurofibrosarcoma, metastatic																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	N	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	−	−	−	+	+	+	+	+	+
Squamous cell papilloma																									
Adenocarcinoma, NOS																					X				
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																X									
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																		X					X		
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+
Papillary adenoma																									
Follicular cell adenoma																									
Parathyroid	−	+	+	−	−	−	−	−	−	+	+	+	+	+	−	+	−	−	−	−	+	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Interstitial cell tumor																X									
Prostate	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																	X								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, unclear primary or metastatic																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	0 0 8	0 1 0	0 1 2	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 5	0 2 8	0 2 9	0 3 0	0 3 2	0 3 4	0 3 6	0 3 7	0 3 9	0 4 0	0 4 2	0 4 4	0 4 5	0 4 7	0 4 9	0 5 0	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																			X							1
Fibrosarcoma																										3
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic								X																		2
Alveolar/bronchiolar adenoma			X															X								2
Sarcoma, NOS, metastatic																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																X										3
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	–	–	+	–	+	–		30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular adenoma	X	X		X		X	X		X		X		X			X	X		X							16
Hepatocellular carcinoma		X	X		X			X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	32
Hepatoblastoma															X		X	X								4
Neurofibrosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell papilloma																				X						1
Adenocarcinoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
Malignant lymphoma, lymphocytic type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma													X													1
Pheochromocytoma			X																							3
Pheochromocytoma, malignant																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papillary adenoma															X											1
Follicular cell adenoma					X				X					X												3
Parathyroid	+	+	–	+	+	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, unclear primary or meta																							X			1
Malignant lymphoma, mixed type									X			X		X		X				X					X	6

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	25.2%	5.8%	8.3%
Terminal Rates (c)	4/28 (14%)	1/32 (3%)	1/31 (3%)
Week of First Observation	59	93	90
Life Table Tests (d)	P=0.031N	P=0.027N	P=0.065N
Incidental Tumor Tests (d)	P=0.075N	P=0.097N	P=0.101N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.026N	P=0.061N
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	9/50 (18%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	25.2%	5.8%	14.0%
Terminal Rates (c)	4/28 (14%)	1/32 (3%)	2/31 (6%)
Week of First Observation	59	93	90
Life Table Tests (d)	P=0.130N	P=0.027N	P=0.195N
Incidental Tumor Tests (d)	P=0.285N	P=0.097N	P=0.334N
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.026N	P=0.194N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/50 (20%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	27.6%	5.8%	11.4%
Terminal Rates (c)	4/28 (14%)	1/32 (3%)	2/31 (6%)
Week of First Observation	59	93	90
Life Table Tests (d)	P=0.039N	P=0.016N	P=0.078N
Incidental Tumor Tests (d)	P=0.106N	P=0.070N	P=0.147N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.014N	P=0.074N
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	10/50 (20%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	27.6%	5.8%	16.9%
Terminal Rates (c)	4/28 (14%)	1/32 (3%)	3/31 (10%)
Week of First Observation	59	93	90
Life Table Tests (d)	P=0.141N	P=0.016N	P=0.206N
Incidental Tumor Tests (d)	P=0.333N	P=0.070N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.141N		
Fisher Exact Test (d)		P=0.014N	P=0.207N
Integumentary System: Fibroma, Neurofibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	10/50 (20%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	27.6%	8.9%	16.9%
Terminal Rates (c)	4/28 (14%)	2/32 (6%)	3/31 (10%)
Week of First Observation	59	93	90
Life Table Tests (d)	P=0.144N	P=0.035N	P=0.206N
Incidental Tumor Tests (d)	P=0.333N	P=0.134N	P=0.392N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test (d)		P=0.036N	P=0.207N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	17.8%	25.0%	6.5%
Terminal Rates (c)	3/28 (11%)	8/32 (25%)	2/31 (6%)
Week of First Observation	88	104	104
Life Table Tests (d)	P=0.100N	P=0.470	P=0.121N
Incidental Tumor Tests (d)	P=0.108N	P=0.379	P=0.129N
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.387	P=0.135N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	0.0%	15.2%	0.0%
Terminal Rates (c)	0/28 (0%)	4/32 (13%)	0/31 (0%)
Week of First Observation		103	
Life Table Tests (d)	P=0.575N	P=0.047	(e)
Incidental Tumor Tests (d)	P=0.558	P=0.028	(e)
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.028	(e)
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	13/50 (26%)	2/50 (4%)
Adjusted Rates (b)	17.8%	39.4%	6.5%
Terminal Rates (c)	3/28 (11%)	12/32 (38%)	2/31 (6%)
Week of First Observation	88	103	104
Life Table Tests (d)	P=0.116N	P=0.105	P=0.121N
Incidental Tumor Tests (d)	P=0.150N	P=0.054	P=0.129N
Cochran-Armitage Trend Test (d)	P=0.157N		
Fisher Exact Test (d)		P=0.062	P=0.135N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	8/50 (16%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	24.6%	21.1%	19.4%
Terminal Rates (c)	5/28 (18%)	6/32 (19%)	6/31 (19%)
Week of First Observation	85	101	104
Life Table Tests (d)	P=0.276N	P=0.410N	P=0.336N
Incidental Tumor Tests (d)	P=0.378N	P=0.571N	P=0.418N
Cochran-Armitage Trend Test (d)	P=0.333N		
Fisher Exact Test (d)		P=0.500N	P=0.387N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	26.7%	23.5%	21.6%
Terminal Rates (c)	5/28 (18%)	6/32 (19%)	6/31 (19%)
Week of First Observation	85	101	91
Life Table Tests (d)	P=0.292N	P=0.409N	P=0.353N
Incidental Tumor Tests (d)	P=0.455N	P=0.567	P=0.461N
Cochran-Armitage Trend Test (d)	P=0.341N		
Fisher Exact Test (d)		P=0.500N	P=0.393N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	16.1%	12.0%	9.1%
Terminal Rates (c)	3/28 (11%)	3/32 (9%)	2/31 (6%)
Week of First Observation	97	98	91
Life Table Tests (d)	P=0.265N	P=0.435N	P=0.333N
Incidental Tumor Tests (d)	P=0.389N	P=0.608N	P=0.440N
Cochran-Armitage Trend Test (d)	P=0.290N		
Fisher Exact Test (d)		P=0.500N	P=0.358N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	5/50 (10%)	13/49 (27%)	16/50 (32%)
Adjusted Rates (b)	15.0%	39.4%	46.4%
Terminal Rates (c)	3/28 (11%)	12/32 (38%)	13/31 (42%)
Week of First Observation	85	103	88
Life Table Tests (d)	P=0.009	P=0.058	P=0.012
Incidental Tumor Tests (d)	P=0.010	P=0.035	P=0.015
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		P=0.030	P=0.006

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	14/50 (28%)	11/49 (22%)	32/50 (64%)
Adjusted Rates (b)	37.5%	28.5%	81.9%
Terminal Rates (c)	7/28 (25%)	5/32 (16%)	24/31 (77%)
Week of First Observation	74	80	84
Life Table Tests (d)	P<0.001	P=0.280N	P=0.002
Incidental Tumor Tests (d)	P<0.001	P=0.570	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.343N	P<0.001
Liver: Hepatoblastoma			
Overall Rates (a)	0/50 (0%)	0/49 (0%)	(f) 4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	11.9%
Terminal Rates (c)	0/28 (0%)	0/32 (0%)	3/31 (10%)
Week of First Observation			88
Life Table Tests (d)	P=0.017	(e)	P=0.074
Incidental Tumor Tests (d)	P=0.022	(e)	P=0.085
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.059
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	22/49 (45%)	40/50 (80%)
Adjusted Rates (b)	43.4%	57.6%	100.0%
Terminal Rates (c)	8/28 (29%)	16/32 (50%)	31/31 (100%)
Week of First Observation	74	80	84
Life Table Tests (d)	P<0.001	P=0.324	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.047	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.183	P<0.001
Adrenal Capsule or Adrenal Gland: Adenoma or Cortical Adenoma			
Overall Rates (a)	0/47 (0%)	4/48 (8%)	1/49 (2%)
Adjusted Rates (b)	0.0%	12.5%	3.2%
Terminal Rates (c)	0/27 (0%)	4/32 (13%)	1/31 (3%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.437	P=0.085	P=0.528
Incidental Tumor Tests (d)	P=0.437	P=0.085	P=0.528
Cochran-Armitage Trend Test (d)	P=0.405		
Fisher Exact Test (d)		P=0.061	P=0.510
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/47 (0%)	2/48 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	6.1%	9.3%
Terminal Rates (c)	0/27 (0%)	1/32 (3%)	2/31 (6%)
Week of First Observation		103	95
Life Table Tests (d)	P=0.094	P=0.277	P=0.136
Incidental Tumor Tests (d)	P=0.028	P=0.181	P=0.063
Cochran-Armitage Trend Test (d)	P=0.088		
Fisher Exact Test (d)		P=0.253	P=0.129
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	0/47 (0%)	2/48 (4%)	4/49 (8%)
Adjusted Rates (b)	0.0%	6.1%	12.4%
Terminal Rates (c)	0/27 (0%)	1/32 (3%)	3/31 (10%)
Week of First Observation		103	95
Life Table Tests (d)	P=0.044	P=0.277	P=0.076
Incidental Tumor Tests (d)	P=0.012	P=0.181	P=0.035
Cochran-Armitage Trend Test (d)	P=0.040		
Fisher Exact Test (d)		P=0.253	P=0.064

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/47 (2%)	1/48 (2%)	3/47 (6%)
Adjusted Rates (b)	3.6%	2.9%	9.7%
Terminal Rates (c)	1/28 (4%)	0/32 (0%)	3/31 (10%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.217	P=0.739N	P=0.341
Incidental Tumor Tests (d)	P=0.132	P=0.703	P=0.341
Cochran-Armitage Trend Test (d)	P=0.201		
Fisher Exact Test (d)		P=0.747N	P=0.308
Thyroid Gland: Follicular Cell Adenoma or Papillary Adenoma			
Overall Rates (a)	1/47 (2%)	1/48 (2%)	4/47 (9%)
Adjusted Rates (b)	3.6%	2.9%	12.9%
Terminal Rates (c)	1/28 (4%)	0/32 (0%)	4/31 (13%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.112	P=0.739N	P=0.209
Incidental Tumor Tests (d)	P=0.062	P=0.703	P=0.209
Cochran-Armitage Trend Test (d)	P=0.100		
Fisher Exact Test (d)		P=0.747N	P=0.181
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/47 (2%)	2/48 (4%)	3/47 (6%)
Adjusted Rates (b)	3.6%	5.9%	9.7%
Terminal Rates (c)	1/28 (4%)	1/32 (3%)	3/31 (10%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.242	P=0.538	P=0.341
Incidental Tumor Tests (d)	P=0.158	P=0.453	P=0.341
Cochran-Armitage Trend Test (d)	P=0.221		
Fisher Exact Test (d)		P=0.508	P=0.308
Thyroid Gland: Papillary Adenoma, Follicular Cell Adenoma, or Follicular Cell Carcinoma			
Overall Rates (a)	1/47 (2%)	2/48 (4%)	4/47 (9%)
Adjusted Rates (b)	3.6%	5.9%	12.9%
Terminal Rates (c)	1/28 (4%)	1/32 (3%)	4/31 (13%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.132	P=0.538	P=0.209
Incidental Tumor Tests (d)	P=0.080	P=0.453	P=0.209
Cochran-Armitage Trend Test (d)	P=0.117		
Fisher Exact Test (d)		P=0.508	P=0.181

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups.
(f) All hepatoblastomas were observed in animals also bearing hepatocellular carcinomas.

TABLE C4a. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/50	2/50	6/50
1,2-Dichlorobenzene	4/50	4/50	8/50
Benzene	6/50	5/50	10/50
TOTAL	14/150 (9.3%)	11/150 (7.3%)	24/150 (16.0%)
SD (b)	2.31%	3.06%	4.00%
Range (c)			
High	6/50	5/50	10/50
Low	4/50	2/50	6/50
Overall Historical Incidence			
TOTAL	111/1,093 (10.2%)	63/1,093 (5.8%)	169/1,093 (15.5%)
SD (b)	4.27%	3.82%	5.95%
Range (c)			
High	10/50	6/50	13/50
Low	1/50	0/50	2/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No hepatoblastomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	5/50	12/50	16/50
1,2-Dichlorobenzene	8/50	14/50	19/50
Benzene	7/50	9/50	15/50
TOTAL	20/150 (13.3%)	35/150 (23.3%)	50/150 (33.3%)
SD (b)	3.06%	5.03%	4.16%
Range (c)			
High	8/50	14/50	19/50
Low	5/50	9/50	15/50
Overall Historical Incidence			
TOTAL	140/1,091 (12.8%)	238/1,091 (21.8%)	357/1,091 (32.7%)
SD (b)	6.82%	7.75%	9.63%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	5/50	7/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No hepatoblastomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4c. HISTORICAL INCIDENCE OF ADRENAL GLAND PHEOCHROMOCYTOMAS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	2/50
1,2-Dichlorobenzene	4/50
Benzene	1/48
TOTAL	7/148 (4.7%)
SD (b)	3.02%
Range (c)	
High	4/50
Low	1/48
Overall Historical Incidence	
TOTAL	(d) 23/1,051 (2.2%)
SD (b)	3.10%
Range (c)	
High	5/49
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two pheochromocytomas, malignant

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Wound, NOS	1 (2%)		
Ulcer, NOS	1 (2%)		1 (2%)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	
Fibrosis, multifocal	2 (4%)		
Parasitism	2 (4%)		1 (2%)
Hyperkeratosis	†2 (4%)	1 (2%)	4 (8%)
Acanthosis	2 (4%)		4 (8%)
*Subcutaneous tissue	(50)	(50)	(50)
Foreign body, NOS		2 (4%)	
Abscess, NOS		1 (2%)	
Inflammation, active chronic	1 (2%)		2 (4%)
Inflammation, granulomatous focal	1 (2%)		
Fibrosis, focal			2 (4%)
Fibrosis, multifocal	1 (2%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Peritracheal tissue	(50)	(48)	(47)
Foreign body, NOS	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute diffuse	1 (2%)		
#Bronchial mucous gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		1 (2%)
#Lung/bronchiole	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	4 (8%)	5 (10%)	
#Lung	(50)	(50)	(50)
Aspiration, foreign body		4 (8%)	10 (20%)
Mineralization			1 (2%)
Congestion, NOS	2 (4%)	1 (2%)	2 (4%)
Congestion, acute	1 (2%)	3 (6%)	2 (4%)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, interstitial	7 (14%)	3 (6%)	3 (6%)
Pneumonia, aspiration		1 (2%)	
Pneumonia, interstitial chronic		1 (2%)	
Inflammation, granulomatous focal		3 (6%)	7 (14%)
Hyperplasia, alveolar epithelium	1 (2%)	6 (12%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(49)
Hyperplasia, granulocytic	9 (18%)	3 (6%)	7 (14%)
#Spleen	(47)	(48)	(46)
Depletion, lymphoid	1 (2%)		2 (4%)
#Splenic follicles	(47)	(48)	(46)
Degeneration, NOS		1 (2%)	1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, focal	1 (2%)	4 (8%)	5 (11%)
Hyperplasia, lymphoid	12 (26%)	16 (33%)	17 (37%)
#Splenic red pulp	(47)	(48)	(46)
Hematopoiesis	10 (21%)	6 (13%)	5 (11%)
#Lymph node	(46)	(41)	(47)
Hyperplasia, lymphoid			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(46)	(41)	(47)
Hemorrhage	1 (2%)		
Inflammation, granulomatous focal	1 (2%)	1 (2%)	
Necrosis, focal		1 (2%)	
Depletion, lymphoid		1 (2%)	
Hyperplasia, focal			1 (2%)
Plasmacytosis	3 (7%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)	12 (29%)	10 (21%)
#Lumbar lymph node	(46)	(41)	(47)
Hematopoiesis		1 (2%)	
#Mesenteric lymph node	(46)	(41)	(47)
Inflammation, granulomatous focal	1 (2%)		
Depletion, lymphoid			1 (2%)
Hyperplasia, focal			2 (4%)
Angiectasis	8 (17%)	6 (15%)	18 (38%)
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	5 (11%)	7 (17%)	5 (11%)
Hematopoiesis	10 (22%)	5 (12%)	14 (30%)
#Inguinal lymph node	(46)	(41)	(47)
Hyperplasia, lymphoid		1 (2%)	
#Lung/bronchiole	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Salivary gland	(50)	(50)	(48)
Hyperplasia, lymphoid		2 (4%)	
#Liver	(50)	(49)	(50)
Hematopoiesis			3 (6%)
#Kidney	(50)	(50)	(47)
Hyperplasia, lymphoid			2 (4%)
*Epididymis	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(37)	(39)	(30)
Foreign body, NOS			1 (3%)
Inflammation, acute/chronic			1 (3%)
Depletion, lymphoid	1 (3%)	1 (3%)	6 (20%)
Hyperplasia, lymphoid			1 (3%)
#Thymic cortex	(37)	(39)	(30)
Degeneration, NOS		1 (3%)	
Depletion, lymphoid	4 (11%)	3 (8%)	2 (7%)
#Thymic lymphocytes	(37)	(39)	(30)
Degeneration, NOS		1 (3%)	
Necrosis, focal		1 (3%)	
Necrosis, diffuse		1 (3%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis		1 (2%)	
#Lung	(50)	(50)	(50)
Perivasculitis	1 (2%)		
#Heart	(50)	(50)	(50)
Periarteritis			1 (2%)
#Myocardium	(50)	(50)	(50)
Inflammation, acute focal		2 (4%)	
Inflammation, acute/chronic			1 (2%)
Degeneration, NOS			2 (4%)
Metamorphosis, fatty	1 (2%)		
#Myocardium/right ventricle	(50)	(50)	(50)
Mineralization			1 (2%)
*Sup. pancreaticoduodenal artery	(50)	(50)	(50)
Periarteritis	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
*Mesentery	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		1 (2%)
#Kidney	(50)	(50)	(47)
Periarteritis			1 (2%)
#Kidney/glomerulus	(50)	(50)	(47)
Embolus, fat		1 (2%)	
#Periprostatic tissue	(49)	(50)	(47)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(48)
Foreign body, NOS		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
Degeneration, NOS		1 (2%)	
Necrosis, focal		1 (2%)	
#Liver	(50)	(49)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute focal	1 (2%)		
Necrosis, coagulative	4 (8%)	2 (4%)	6 (12%)
Basophilic cyto change		1 (2%)	
Focal cellular change	3 (6%)	2 (4%)	2 (4%)
Clear cell change	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal			1 (2%)
Angiectasis			1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)
Degeneration, NOS		36 (73%)	39 (78%)
Necrosis, focal	1 (2%)	35 (71%)	37 (74%)
Clear cell change			1 (2%)
Cell size alteration		38 (78%)	40 (80%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)	1 (2%)	4 (8%)
#Bile duct	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
Multiple cysts		1 (2%)	1 (2%)
Hyperplasia, focal		1 (2%)	5 (10%)
#Pancreas	(50)	(49)	(46)
Cystic ducts	1 (2%)		1 (2%)
Inflammation, acute/chronic	1 (2%)		
#Pancreatic acinus	(50)	(49)	(46)
Atrophy, focal		2 (4%)	
*Jejunal lumen	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Esophagus	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
#Periesophageal tissue	(50)	(50)	(50)
Foreign body, NOS	1 (2%)	6 (12%)	5 (10%)
Hemorrhage	1 (2%)		
Inflammation, acute/chronic	1 (2%)	4 (8%)	5 (10%)
Inflammation, granulomatous focal		1 (2%)	
#Glandular stomach	(45)	(46)	(44)
Erosion	1 (2%)		
Hyperplasia, epithelial			1 (2%)
Metaplasia, squamous			1 (2%)
Dysplasia	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(45)	(46)	(44)
Inflammation, active chronic			1 (2%)
Hyperplasia, epithelial	2 (4%)		
Hyperkeratosis	3 (7%)	1 (2%)	3 (7%)
Acanthosis	3 (7%)	1 (2%)	3 (7%)
#Peyer's patch	(44)	(43)	(44)
Inflammation, active chronic			1 (2%)
#Jejunum	(44)	(43)	(44)
Ulcer, NOS			1 (2%)
Necrosis, focal			1 (2%)
#Ileum	(44)	(43)	(44)
Inflammation, acute focal	1 (2%)		
#Colon	(46)	(43)	(44)
Parasitism		1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(47)
Mineralization	1 (2%)		
Inflammation, interstitial		1 (2%)	
Pyelonephritis, acute			1 (2%)
Pyelonephritis, acute/chronic		1 (2%)	1 (2%)
Nephropathy	6 (12%)	12 (24%)	15 (32%)
Infarct, acute			1 (2%)
#Kidney/cortex	(50)	(50)	(47)
Cyst, NOS	1 (2%)	2 (4%)	
Infarct, focal		1 (2%)	
#Kidney/tubule	(50)	(50)	(47)
Dilatation, NOS			1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Regeneration, NOS	24 (48%)	20 (40%)	17 (36%)
#Urinary bladder	(46)	(47)	(44)
Dilatation, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		
Hyperplasia, epithelial			1 (2%)
#Urinary bladder/mucosa	(46)	(47)	(44)
Cytoplasmic vacuolization			1 (2%)
#Urinary bladder/submucosa	(46)	(47)	(44)
Congestion, NOS	1 (2%)		
#Urinary bladder/muscularis	(46)	(47)	(44)
Inflammation, acute focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(41)	(43)	(45)
Multiple cysts			1 (2%)
#Adrenal/capsule	(47)	(48)	(49)
Accessory structure			1 (2%)
Hyperplasia, focal	11 (23%)	21 (44%)	28 (57%)
#Adrenal cortex	(47)	(48)	(49)
Cyst, NOS	1 (2%)		
Hemorrhage		1 (2%)	
Infarct, acute			1 (2%)
Cytoplasmic vacuolization			2 (4%)
Clear cell change	1 (2%)		
Hypertrophy, focal	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, focal	1 (2%)	3 (6%)	1 (2%)
#Adrenal medulla	(47)	(48)	(49)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	2 (4%)	3 (6%)	4 (8%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Thyroid	(47)	(48)	(47)
Follicular cyst, NOS	2 (4%)	1 (2%)	
Hyperplasia, C-cell			1 (2%)
Hyperplasia, follicular cell	1 (2%)	4 (8%)	10 (21%)
#Pancreatic islets	(50)	(49)	(46)
Hyperplasia, focal	6 (12%)	3 (6%)	4 (9%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	
Cyst, NOS	1 (2%)		
Multiple cysts			1 (2%)
Cystic ducts			1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, active chronic	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic suppurative	1 (2%)		1 (2%)
#Prostate	(49)	(50)	(47)
Inflammation, acute focal	1 (2%)	1 (2%)	
Inflammation, acute diffuse			1 (2%)
Hyperplasia, epithelial			2 (4%)
*Seminal vesicle	(50)	(50)	(50)
Retention fluid	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, epithelial	1 (2%)		1 (2%)
#Periprostatic tissue	(49)	(50)	(47)
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute diffuse	1 (2%)		
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Thrombophlebitis		1 (2%)	
#Testis	(50)	(50)	(48)
Inflammation, granulomatous focal		1 (2%)	
Atrophy, NOS	1 (2%)		
Atrophy, diffuse			1 (2%)
Hyperplasia, interstitial cell		1 (2%)	
#Testis/tubule	(50)	(50)	(48)
Degeneration, NOS	1 (2%)		
Atrophy, focal			1 (2%)
*Epididymis	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)	1 (2%)	
Inflammation, granulomatous focal		1 (2%)	1 (2%)
Granuloma, spermatic			1 (2%)
Hyperplasia, epithelial		1 (2%)	
*Vas deferens	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(48)	(47)
Inflammation, chronic focal			1 (2%)
#Brain	(50)	(48)	(47)
Necrosis, focal		1 (2%)	
#Hippocampus	(50)	(48)	(47)
Necrosis, focal		1 (2%)	
#Cerebellum	(50)	(48)	(47)
Cytoplasmic vacuolization			1 (2%)
#Cerebellar white matter	(50)	(48)	(47)
Cytoplasmic vacuolization			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Phthisis bulbi	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, active chronic			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Knee joint	(50)	(50)	(50)
Ankylosing spondylitis		1 (2%)	
*Skeletal muscle	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS	3 (6%)	4 (8%)	7 (14%)
Inflammation, multifocal		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute necrotizing			1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic	2 (4%)	1 (2%)	5 (10%)
*Peritoneum	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
*Parietal peritoneum	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Inflammation, granulomatous focal		1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous focal			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
\# Number of animals examined microscopically at this site
† Multiple occurrence of morphology in the same organ. Tissue is counted once only.

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Osteosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(49)
Hepatocellular carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		
Pheochromocytoma, metastatic	1 (2%)		
Leiomyosarcoma, metastatic			1 (2%)
Osteosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
Malignant lymphoma, lymphocytic type	6 (12%)	4 (8%)	4 (8%)
Malignant lymphoma, histiocytic type	2 (4%)	1 (2%)	4 (8%)
Malignant lymphoma, mixed type	12 (24%)	9 (18%)	12 (24%)
Mast cell sarcoma		1 (2%)	
Leukemia, NOS	1 (2%)		
#Peyer's patch	(47)	(43)	(42)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Mesenteric lymph node	(46)	(43)	(44)
Hemangioma	1 (2%)		
#Liver	(50)	(48)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	1 (2%)		2 (4%)
#Ovary/parovarian	(49)	(48)	(49)
Hemangioma			1 (2%)
#Ovary	(49)	(48)	(49)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(50)
Hepatocellular adenoma	10 (20%)	6 (13%)	21 (42%)
Hepatocellular carcinoma	5 (10%)	5 (10%)	19 (38%)
#Forestomach	(47)	(43)	(43)
Squamous cell papilloma	4 (9%)		1 (2%)
#Pylorus	(47)	(43)	(43)
Adenomatous polyp, NOS	1 (2%)		
#Cecum	(48)	(45)	(45)
Leiomyosarcoma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney/cortex	(50)	(47)	(46)
Tubular cell adenoma		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(42)	(40)
Adenoma, NOS	1 (2%)	1 (2%)	1 (3%)
#Anterior pituitary	(48)	(42)	(40)
Adenoma, NOS	6 (13%)	3 (7%)	6 (15%)
Adenocarcinoma, NOS		1 (2%)	
#Adrenal	(49)	(46)	(49)
Cortical adenoma	1 (2%)	2 (4%)	
#Adrenal/capsule	(49)	(46)	(49)
Adenoma, NOS		2 (4%)	
#Adrenal medulla	(49)	(46)	(49)
Pheochromocytoma		3 (7%)	1 (2%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(45)	(46)
Follicular cell adenoma			3 (7%)
#Pancreatic islets	(48)	(47)	(48)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	1 (2%)
Adenosquamous carcinoma			1 (2%)
Fibroadenoma			1 (2%)
#Uterus	(49)	(47)	(50)
Leiomyoma	1 (2%)		
Endometrial stromal polyp	1 (2%)	1 (2%)	
#Cervix uteri	(49)	(47)	(50)
Leiomyosarcoma			1 (2%)
#Endometrial gland	(49)	(47)	(50)
Papillary adenocarcinoma			1 (2%)
#Ovary	(49)	(48)	(49)
Luteoma	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(48)	(46)
Adenocarcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	
Papillary adenocarcinoma	1 (2%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
*Vertebral column	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
*Muscle of leg	(50)	(50)	(50)
Rhabdomyosarcoma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	6	9
Moribund sacrifice	9	4	3
Terminal sacrifice	35	36	35
Dosing accident	2	4	3
Accidentally killed, NOS	1		
TUMOR SUMMARY			
Total animals with primary tumors**	37	36	46
Total primary tumors	66	54	86
Total animals with benign tumors	24	18	31
Total benign tumors	32	25	39
Total animals with malignant tumors	26	24	33
Total malignant tumors	34	29	47
Total animals with secondary tumors##	2	1	2
Total secondary tumors	2	1	2

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: VEHICLE CONTROL

ANIMAL NUMBER	046	004	023	038	045	011	006	028	009	001	034	026	044	012	018	002	003	005	007	008	010	013	014	015	016
WEEKS ON STUDY	011	012	063	068	074	087	090	090	091	095	095	096	097	100	102	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma, metastatic																									
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+
Hemangioma										X															
Thymus	+	+	−	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X										X			X					
Hepatocellular carcinoma											X			X											
Hemangioma										X															
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Adenomatous polyp, NOS																									
Small intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X										X		
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma, malignant																									
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	−	+	+	+	−	+	−	−	−	+	−	+	−	+	+	+	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	+	+	N	N	N	N	N	N	N	N	+	N	N	+	+	N	N	N	N	N
Adenocarcinoma, NOS																			X						
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								X	
Endometrial stromal polyp																					X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Luteoma																				X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Papillary adenocarcinoma																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Rhabdomyosarcoma																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type						X						X	X					X							
Malignant lymphoma, histiocytic type															X										
Malignant lymphoma, mixed type					X						X											X	X		
Leukemia, NOS			X																						

\+ Tissue examined microscopically
−. Required tissue not examined microscopically
X Tumor incidence
N· Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M. Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0 1 7	0 1 9	0 2 0	0 2 1	0 2 2	0 2 4	0 2 5	0 2 7	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 5	0 3 6	0 3 7	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma		X														X						X			3
Alveolar/bronchiolar carcinoma																					X			X		2
Pheochromocytoma, metastatic							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma																										1
Thymus	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X	X	X		X					X							X			X			10
Hepatocellular carcinoma		X																	X		X					5
Hemangioma																										1
Hemangiosarcoma									X																	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma			X	X																		X			X	4
Adenomatous polyp, NOS									X																	1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma									X																	1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X																X			X	X	X				7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																						X				1
Pheochromocytoma, malignant							X																			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	+	–	–	+	+	–	–	+	+	–	+	+	–	–	+	–	+	+	+	–	+	+	–	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								1
Papillary adenocarcinoma																			X							1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Rhabdomyosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type															X						X				X	6
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type	X	X	X	X	X		X															X	X			12
Leukemia, NOS																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: LOW DOSE

ANIMAL NUMBER	0038	0001	0007	0023	0035	0036	0039	0040	0022	0048	0024	0116	0021	0449	0002	0003	0004	0005	0006	0008	0009	0110	0111	0112	0113
WEEKS ON STUDY	0006	0111	0111	0111	0669	0886	0886	0991	0995	0995	0997	0999	1001	1003	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X					X							X								
Trachea	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	−	−	+	+	+	+	+	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	+	−	+	+	+	+	−	−	−	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X	X						X		
Hepatocellular carcinoma					X							X													
Bile duct	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	+	+	N	N	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	−	−	−	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	−	−	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	−	−	−	−	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	−	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X		X		X
Adenocarcinoma, NOS																									
Adrenal	+	−	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Cortical adenoma																								X	
Pheochromocytoma																X									
Thyroid	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Parathyroid	−	−	−	−	+	+	−	+	+	−	+	+	−	−	−	+	+	−	−	−	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	N	+	N	N	+	+	N	N	+	+	+	N	+	N	+	+	+	+
Adenocarcinoma, NOS												X													
Uterus	+	+	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X		
Papillary adenocarcinoma																				X					
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS										X															
Malignant lymphoma, NOS														X											
Malignant lymphoma, lymphocytic type							X	X			X		X												
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type									X						X	X									
Mast cell sarcoma															X										

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

ANIMAL NUMBER	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 7	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 5 0	TOTAL TISSUES TUMORS
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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																X				X						5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymus	+	+	+	−	+	−	−	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma									X	X		X														6
Hepatocellular carcinoma									X												X		X			5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Malignant lymphoma, mixed type		X																								1
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tubular cell adenoma	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	42
Adenoma, NOS												X														4
Adenocarcinoma, NOS					X																					1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS								X																		2
Cortical adenoma																									X	2
Pheochromocytoma																X				X						3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	45
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	−	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	+	+	+	+	N	N	+	+	N	+	N	N	N	+	N	N	N	N	+	N	N	*50
Adenocarcinoma, NOS							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Endometrial stromal polyp						X																				1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS, invasive					X																					1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
Papillary adenocarcinoma									X																	2
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, lymphocytic type																										4
Malignant lymphoma, histiocytic type											X															1
Malignant lymphoma, mixed type	X		X																	X		X	X	X		9
Mast cell sarcoma																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE: HIGH DOSE

ANIMAL NUMBER	037	034	024	014	032	005	022	012	049	043	020	011	031	016	001	002	003	004	006	007	008	009	010	013	015
WEEKS ON STUDY	010	011	064	065	070	075	083	092	092	093	094	097	100	101	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Leiomyosarcoma, metastatic																		X							
Osteosarcoma, metastatic										X															
Trachea	+	+	+	−	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	−	+	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X					X	X	X	X	X		X				X	
Hepatocellular carcinoma							X						X	X						X		X	X	X	X
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	N	N	+	N	N	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	−	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	−	−	+	−	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	−	−	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	−	−	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS			X																			X			X
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
Parathyroid	+	+	+	−	+	−	+	+	−	−	−	+	+	−	+	+	−	−	+	−	+	+	+	+	−
Pancreatic islets	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X														
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	+	N	N	N	N	+	N
Adenocarcinoma, NOS																									
Adenosquamous carcinoma			X																						
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenocarcinoma																									
Leiomyosarcoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																									
Hemangioma						X													X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma							X																		
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, histiocytic type								X											X					X	
Malignant lymphoma, mixed type				X					X				X							X		X			X

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

ANIMAL NUMBER	0017	0018	0019	0021	0023	0025	0026	0027	0028	0029	0030	0033	0035	0036	0038	0039	0040	0041	0042	0044	0045	0046	0047	0048	0050	TOTAL TISSUES TUMORS
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	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Leiomyosarcoma, metastatic																										1
Osteosarcoma, metastatic																										1
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X			X		X	X	X	X		X	X	X	X	X				X		X	21
Hepatocellular carcinoma	X		X			X	X		X					X			X			X	X	X		X		19
Hemangiosarcoma						X												X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Squamous cell papilloma																			X							1
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+		40
Adenoma, NOS		X										X			X					X						7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																									X	1
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma												X			X											3
Parathyroid	−	+	+	−	−	+	−	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	27
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	+	N	N	+	+	N	N	+	N	+	+	N	+	N	N	+	N	N	+	N	N	*50
Adenocarcinoma, NOS				X																						1
Adenosquamous carcinoma																										1
Fibroadenoma												X														1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary adenocarcinoma																								X		1
Leiomyosarcoma																										1
Ovary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma			X																							1
Hemangioma																										2
NERVOUS SYSTEM																										
Brain	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, lymphocytic type						X				X											X					4
Malignant lymphoma, histiocytic type									X																	4
Malignant lymphoma, mixed type		X						X						X				X	X					X		12

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	Vehicle Control	300 mg/kg	600 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	5/48 (10%)	1/49 (2%)
Adjusted Rates (b)	8.6%	12.5%	2.8%
Terminal Rates (c)	3/35 (9%)	3/36 (8%)	1/36 (3%)
Week of First Observation	104	69	104
Life Table Tests (d)	P=0.258N	P=0.371	P=0.295N
Incidental Tumor Tests (d)	P=0.251N	P=0.300	P=0.295N
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test (d)		P=0.335	P=0.316N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	5/48 (10%)	1/49 (2%)
Adjusted Rates (b)	14.3%	12.5%	2.8%
Terminal Rates (c)	5/35 (14%)	3/36 (8%)	1/36 (3%)
Week of First Observation	104	69	104
Life Table Tests (d)	P=0.086N	P=0.614N	P=0.096N
Incidental Tumor Tests (d)	P=0.084N	P=0.581	P=0.096N
Cochran-Armitage Trend Test (d)	P=0.095N		
Fisher Exact Test (d)		P=0.603	P=0.107N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	15.7%	9.3%	10.8%
Terminal Rates (c)	4/35 (11%)	0/36 (0%)	3/36 (8%)
Week of First Observation	87	86	101
Life Table Tests (d)	P=0.300N	P=0.361N	P=0.360N
Incidental Tumor Tests (d)	P=0.359N	P=0.413N	P=0.399N
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test (d)		P=0.371N	P=0.371N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	5.3%	2.8%	10.5%
Terminal Rates (c)	0/35 (0%)	1/36 (3%)	3/36 (8%)
Week of First Observation	96	104	92
Life Table Tests (d)	P=0.249	P=0.491N	P=0.350
Incidental Tumor Tests (d)	P=0.214	P=0.497N	P=0.295
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	12/50 (24%)
Adjusted Rates (b)	31.8%	26.8%	30.2%
Terminal Rates (c)	10/35 (29%)	9/36 (25%)	9/36 (25%)
Week of First Observation	74	95	65
Life Table Tests (d)	P=0.524N	P=0.378N	P=0.566N
Incidental Tumor Tests (d)	P=0.525N	P=0.425N	P=0.571N
Cochran-Armitage Trend Test (d)	P=0.548		
Fisher Exact Test (d)		P=0.405N	P=0.592N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	20/50 (40%)	16/50 (32%)	20/50 (40%)
Adjusted Rates (b)	48.4%	37.8%	48.4%
Terminal Rates (c)	14/35 (40%)	10/36 (28%)	15/36 (42%)
Week of First Observation	74	86	65
Life Table Tests (d)	P=0.509N	P=0.257N	P=0.542N
Incidental Tumor Tests (d)	P=0.502	P=0.303N	P=0.558
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.266N	P=0.581N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	21/50 (42%)	16/50 (32%)	20/50 (40%)
Adjusted Rates (b)	49.4%	37.8%	48.4%
Terminal Rates (c)	14/35 (40%)	10/36 (28%)	15/36 (42%)
Week of First Observation	63	86	65
Life Table Tests (d)	P=0.434N	P=0.205N	P=0.468N
Incidental Tumor Tests (d)	P=0.487N	P=0.267N	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.204N	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.9%	0.0%	7.7%
Terminal Rates (c)	1/35 (3%)	0/36 (0%)	2/36 (6%)
Week of First Observation	104		83
Life Table Tests (d)	P=0.180	P=0.494N	P=0.312
Incidental Tumor Tests (d)	P=0.167	P=0.494N	P=0.288
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	5.2%	0.0%	12.4%
Terminal Rates (c)	1/35 (3%)	0/36 (0%)	3/36 (8%)
Week of First Observation	95		75
Life Table Tests (d)	P=0.122	P=0.234N	P=0.224
Incidental Tumor Tests (d)	P=0.127	P=0.237N	P=0.217
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test (d)		P=0.248N	P=0.218
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	6/48 (13%)	21/50 (42%)
Adjusted Rates (b)	27.4%	16.7%	55.1%
Terminal Rates (c)	9/35 (26%)	6/36 (17%)	19/36 (53%)
Week of First Observation	90	104	92
Life Table Tests (d)	P=0.008	P=0.187N	P=0.017
Incidental Tumor Tests (d)	P=0.006	P=0.197N	P=0.012
Cochran-Armitage Trend Test (d)	P=0.008		
Fisher Exact Test (d)		P=0.233N	P=0.015
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	5/48 (10%)	19/50 (38%)
Adjusted Rates (b)	13.2%	12.6%	48.6%
Terminal Rates (c)	3/35 (9%)	3/36 (8%)	16/36 (44%)
Week of First Observation	95	69	83
Life Table Tests (d)	P<0.001	P=0.610N	P=0.002
Incidental Tumor Tests (d)	P<0.001	P=0.578	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.603	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	10/48 (21%)	36/50 (72%)
Adjusted Rates (b)	39.0%	25.9%	90.0%
Terminal Rates (c)	12/35 (34%)	8/36 (22%)	32/36 (89%)
Week of First Observation	90	69	83
Life Table Tests (d)	P<0.001	P=0.164N	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.200N	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.210N	P<0.001

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	4/47 (9%)	0/43 (0%)	1/43 (2%)
Adjusted Rates (b)	11.4%	0.0%	2.9%
Terminal Rates (c)	4/35 (11%)	0/36 (0%)	1/35 (3%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.080N	P=0.059N	P=0.178N
Incidental Tumor Tests (d)	P=0.080N	P=0.059N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.096N		
Fisher Exact Test (d)		P=0.070N	P=0.210N
Pituitary Gland: Adenoma			
Overall Rates (a)	6/48 (13%)	3/42 (7%)	6/40 (15%)
Adjusted Rates (b)	17.6%	8.8%	17.9%
Terminal Rates (c)	6/34 (18%)	3/34 (9%)	5/31 (16%)
Week of First Observation	104	104	64
Life Table Tests (d)	P=0.511	P=0.239N	P=0.562
Incidental Tumor Tests (d)	P=0.488	P=0.239N	P=0.536
Cochran-Armitage Trend Test (d)	P=0.444		
Fisher Exact Test (d)		P=0.314N	P=0.486
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	6/48 (13%)	4/42 (10%)	6/40 (15%)
Adjusted Rates (b)	17.6%	11.8%	17.9%
Terminal Rates (c)	6/34 (18%)	4/34 (12%)	5/31 (16%)
Week of First Observation	104	104	64
Life Table Tests (d)	P=0.507	P=0.367N	P=0.562
Incidental Tumor Tests (d)	P=0.484	P=0.367N	P=0.536
Cochran-Armitage Trend Test (d)	P=0.437		
Fisher Exact Test (d)		P=0.458N	P=0.486
Adrenal Capsule or Adrenal Gland: Adenoma or Cortical Adenoma			
Overall Rates (a)	1/49 (2%)	4/46 (9%)	0/49 (0%)
Adjusted Rates (b)	2.9%	11.1%	0.0%
Terminal Rates (c)	1/35 (3%)	4/36 (11%)	0/36 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.380N	P=0.187	P=0.494N
Incidental Tumor Tests (d)	P=0.380N	P=0.187	P=0.494N
Cochran-Armitage Trend Test (d)	P=0.391N		
Fisher Exact Test (d)		P=0.162	P=0.500N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/49 (0%)	3/46 (7%)	1/49 (2%)
Adjusted Rates (b)	0.0%	8.3%	2.8%
Terminal Rates (c)	0/35 (0%)	3/36 (8%)	1/36 (3%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.387	P=0.126	P=0.506
Incidental Tumor Tests (d)	P=0.387	P=0.126	P=0.506
Cochran-Armitage Trend Test (d)	P=0.379		
Fisher Exact Test (d)		P=0.110	P=0.500
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	3/46 (7%)	1/49 (2%)
Adjusted Rates (b)	2.9%	8.3%	2.8%
Terminal Rates (c)	1/35 (3%)	3/36 (8%)	1/36 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.600N	P=0.315	P=0.756N
Incidental Tumor Tests (d)	P=0.600N	P=0.315	P=0.756N
Cochran-Armitage Trend Test (d)	P=0.609		
Fisher Exact Test (d)		P=0.285	P=0.753

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/48 (0%)	0/45 (0%)	3/46 (7%)
Adjusted Rates (b)	0.0%	0.0%	8.6%
Terminal Rates (c)	0/35 (0%)	0/34 (0%)	3/35 (9%)
Week of First Observation			104
Life Table Tests (d)	P=0.038	(e)	P=0.121
Incidental Tumor Tests (d)	P=0.038	(e)	P=0.121
Cochran-Armitage Trend Test (d)	P=0.036		
Fisher Exact Test (d)		(e)	P=0.113
Mammary Gland: Fibroadenoma, Adenocarcinoma, or Adenosquamous Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.9%	5.3%	7.5%
Terminal Rates (c)	1/35 (3%)	1/36 (3%)	2/36 (6%)
Week of First Observation	104	99	64
Life Table Tests (d)	P=0.232	P=0.513	P=0.316
Incidental Tumor Tests (d)	P=0.245	P=0.507	P=0.340
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Harderian Gland: Adenoma or Papillary Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.7%	8.3%	0.0%
Terminal Rates (c)	2/35 (6%)	3/36 (8%)	0/36 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.193N	P=0.513	P=0.232N
Incidental Tumor Tests (d)	P=0.193N	P=0.513	P=0.232N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 300 mg/kg and vehicle control groups.

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	2/50	1/50	2/50
1,2-Dichlorobenzene	2/48	2/48	4/48
Benzene	1/50	3/50	4/50
TOTAL	5/148 (3.4%)	6/148 (4.1%)	10/148 (6.8%)
SD (b)	1.21%	2.00%	2.41%
Range (c)			
High	2/48	3/50	4/48
Low	1/50	1/50	2/50
Overall Historical Incidence			
TOTAL	41/1,092 (3.8%)	34/1,092 (3.1%)	74/1,092 (6.8%)
SD (b)	2.65%	2.29%	3.63%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No hepatoblastomas have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	(b) 2/42	0/42	(b) 2/42
1,2-Dichlorobenzene	1/43	0/43	1/43
Benzene	3/49	0/49	3/49
TOTAL	6/134 (4.5%)	0/134 (0.0%)	6/134 (4.5%)
SD (c)	1.92%	0.00%	1.92%
Range (d)			
High	3/49	0/49	3/49
Low	1/43	0/49	1/43
Overall Historical Incidence			
TOTAL	(e) 36/1,009 (3.6%)	5/1,009 (0.5%)	(e) 40/1,009 (4.0%)
SD (c)	3.01%	1.10%	3.04%
Range (d)			
High	5/50	2/49	5/50
Low	0/49	0/50	0/47

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes papillary adenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papillary adenoma, one cystadenoma, and two papillary cystadenomas

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Cystic ducts		1 (2%)	
Inflammation, active chronic		1 (2%)	
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(48)	(49)
Lymphocytic inflammatory infiltrate	6 (12%)	5 (10%)	6 (12%)
Inflammation, acute/chronic	1 (2%)		
#Lung	(50)	(48)	(49)
Aspiration, foreign body		2 (4%)	3 (6%)
Congestion, NOS			1 (2%)
Congestion, acute			1 (2%)
Edema, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, interstitial			3 (6%)
Pneumonia, aspiration	1 (2%)		
Inflammation, active chronic			1 (2%)
Inflammation, acute/chronic	3 (6%)		
Inflammation, granulomatous focal	5 (10%)	2 (4%)	3 (6%)
Hyperplasia, alveolar epithelium	1 (2%)		1 (2%)
#Lung/alveoli	(50)	(48)	(49)
Hemorrhage	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#Lateral ventricle	(50)	(48)	(46)
Hyperplasia, lymphoid	1 (2%)		
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid		5 (10%)	
#Bone marrow	(46)	(48)	(49)
Metamorphosis, fatty			2 (4%)
Myelofibrosis	2 (4%)	4 (8%)	1 (2%)
Hyperplasia, granulocytic	4 (9%)	1 (2%)	5 (10%)
Hyperplasia, reticulum cell			1 (2%)
#Spleen	(50)	(48)	(46)
Degeneration, NOS			1 (2%)
Depletion, lymphoid		1 (2%)	
#Splenic follicles	(50)	(48)	(46)
Hyperplasia, focal	2 (4%)	2 (4%)	10 (22%)
Hyperplasia, lymphoid	14 (28%)	15 (31%)	10 (22%)
#Splenic red pulp	(50)	(48)	(46)
Hematopoiesis	2 (4%)	1 (2%)	4 (9%)
#Lymph node	(46)	(43)	(44)
Cyst, NOS			1 (2%)
Inflammation, NOS			1 (2%)
#Mandibular lymph node	(46)	(43)	(44)
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)		
Necrosis, focal			1 (2%)
Hyperplasia, focal			1 (2%)
Hyperplasia, lymphoid	3 (7%)	8 (19%)	10 (23%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(46)	(43)	(44)
Cyst, NOS			1 (2%)
Angiectasis		2 (5%)	5 (11%)
Histiocytosis	1 (2%)		
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (5%)	3 (7%)
Hematopoiesis	1 (2%)	1 (2%)	3 (7%)
#Inguinal lymph node	(46)	(43)	(44)
Necrosis, diffuse		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Thymic lymph node	(46)	(43)	(44)
Hemorrhage	1 (2%)		
Inflammation, acute focal			1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Lung/bronchiole	(50)	(48)	(49)
Hyperplasia, lymphoid	5 (10%)		2 (4%)
#Lung	(50)	(48)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Mastocytosis			1 (2%)
#Salivary gland	(50)	(47)	(48)
Hyperplasia, lymphoid			2 (4%)
#Liver	(50)	(48)	(50)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis		3 (6%)	1 (2%)
#Peyer's patch	(47)	(43)	(42)
Hyperplasia, lymphoid		3 (7%)	
#Kidney	(50)	(47)	(46)
Hyperplasia, lymphoid			1 (2%)
#Urinary bladder	(47)	(43)	(43)
Hyperplasia, lymphoid		3 (7%)	3 (7%)
#Adrenal cortex	(49)	(46)	(49)
Hematopoiesis			1 (2%)
#Thymus	(43)	(36)	(42)
Foreign body, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, lymphoid		2 (6%)	2 (5%)
#Thymic cortex	(43)	(36)	(42)
Degeneration, NOS	1 (2%)		
Depletion, lymphoid	1 (2%)	1 (3%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Myocardium	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Periarteritis			1 (2%)
Degeneration, NOS			1 (2%)
Metamorphosis, fatty	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(47)	(48)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute/chronic			1 (2%)
Atrophy, focal			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(48)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	4 (8%)	2 (4%)	4 (8%)
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous focal			2 (4%)
Necrosis, coagulative	2 (4%)	2 (4%)	3 (6%)
Infarct, NOS			1 (2%)
Metamorphosis, fatty	1 (2%)		
Focal cellular change	2 (4%)		2 (4%)
#Liver/centrilobular	(50)	(48)	(50)
Cytoplasmic vacuolization		1 (2%)	
#Liver/periportal	(50)	(48)	(50)
Inflammation, acute/chronic	1 (2%)		
#Liver/Kupffer cell	(50)	(48)	(50)
Hyperplasia, focal			1 (2%)
#Liver/hepatocytes	(50)	(48)	(50)
Degeneration, NOS		8 (17%)	36 (72%)
Necrosis, focal	1 (2%)	4 (8%)	30 (60%)
Focal cellular change	1 (2%)		
Cell size alteration		4 (8%)	27 (54%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, papillary	1 (2%)		
#Bile duct	(50)	(48)	(50)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Pancreas	(48)	(47)	(48)
Inflammation, active chronic			1 (2%)
Inflammation, granulomatous focal			1 (2%)
#Pancreatic acinus	(48)	(47)	(48)
Atrophy, focal	3 (6%)	4 (9%)	
Hyperplasia, focal			1 (2%)
#Pancreas/interstitiu	(48)	(47)	(48)
Inflammation, active chronic			1 (2%)
#Esophagus	(50)	(50)	(50)
Lacerated wound		1 (2%)	
#Periesophageal tissue	(50)	(50)	(50)
Foreign body, NOS	2 (4%)	3 (6%)	1 (2%)
Inflammation, multifocal		1 (2%)	
Inflammation, acute			1 (2%)
Inflammation, acute/chronic	1 (2%)	2 (4%)	1 (2%)
#Glandular stomach	(47)	(43)	(43)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Inflammation, acute focal	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Hyperplasia, focal	1 (2%)		1 (2%)
Metaplasia, squamous	2 (4%)		
#Forestomach	(47)	(43)	(43)
Ulcer, NOS	1 (2%)		
Inflammation, acute focal		1 (2%)	
Ulcer, chronic			1 (2%)
Hyperplasia, epithelial	2 (4%)		
Hyperkeratosis		1 (2%)	
Acanthosis		1 (2%)	1 (2%)
#Peyer's patch	(47)	(43)	(42)
Inflammation, granulomatous focal	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Jejunum	(47)	(43)	(42)
Ulcer, NOS	1 (2%)		
Necrosis, NOS			1 (2%)
#Jejunal mucosa	(47)	(43)	(42)
Inflammation, acute/chronic	1 (2%)		
Amyloidosis, focal			1 (2%)
#Colon	(48)	(45)	(45)
Inflammation, acute/chronic	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(47)	(46)
Glomerulonephritis, acute			1 (2%)
Nephropathy		3 (6%)	3 (7%)
Infarct, NOS	1 (2%)		
#Kidney/cortex	(50)	(47)	(46)
Infarct, focal		2 (4%)	
Metaplasia, osseous	1 (2%)		
#Kidney/tubule	(50)	(47)	(46)
Dilatation, NOS			1 (2%)
Hyperplasia, epithelial			1 (2%)
Regeneration, NOS	4 (8%)	7 (15%)	13 (28%)
#Urinary bladder	(47)	(43)	(43)
Hemorrhage			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(42)	(40)
Congestion, NOS	1 (2%)		2 (5%)
Hyperplasia, focal	15 (31%)	12 (29%)	9 (23%)
#Adrenal/capsule	(49)	(46)	(49)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal	37 (76%)	43 (93%)	39 (80%)
#Adrenal cortex	(49)	(46)	(49)
Congestion, NOS			1 (2%)
Metamorphosis, fatty			1 (2%)
Cytoplasmic vacuolization			3 (6%)
Hypertrophy, focal			1 (2%)
Hyperplasia, focal		1 (2%)	1 (2%)
#Adrenal medulla	(49)	(46)	(49)
Hyperplasia, focal		1 (2%)	
#Thyroid	(48)	(45)	(46)
Follicular cyst, NOS	1 (2%)	1 (2%)	4 (9%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Hyperplasia, C-cell	1 (2%)		
Hyperplasia, follicular cell	8 (17%)	5 (11%)	9 (20%)
#Thyroid follicle	(48)	(45)	(46)
Multiple cysts		3 (7%)	
#Pancreatic islets	(48)	(47)	(48)
Hyperplasia, focal	3 (6%)	2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts		3 (6%)	1 (2%)
*Vagina	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
Erosion			1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(49)	(47)	(50)
Dilatation, NOS	1 (2%)		2 (4%)
Cyst, NOS			1 (2%)
Hematoma, organized	1 (2%)		
Pyometra	1 (2%)		
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse		1 (2%)	
Inflammation, active chronic			1 (2%)
Hyperplasia, epithelial	1 (2%)		
Metaplasia, squamous			1 (2%)
Adenomyosis	1 (2%)		
#Cervix uteri	(49)	(47)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, active chronic			1 (2%)
#Uterus/endometrium	(49)	(47)	(50)
Angiectasis		1 (2%)	
#Endometrial gland	(49)	(47)	(50)
Cyst, NOS			1 (2%)
Multiple cysts		1 (2%)	
Hematoma, organized		1 (2%)	
Hyperplasia, focal	1 (2%)		
Hyperplasia, cystic	43 (88%)	40 (85%)	40 (80%)
Metaplasia, squamous		2 (4%)	
#Endometrial stroma	(49)	(47)	(50)
Inflammation, acute focal	1 (2%)		
#Fallopian tube	(49)	(47)	(50)
Hyperplasia, epithelial	1 (2%)		
#Ovary/parovarian	(49)	(48)	(49)
Inflammation, suppurative			1 (2%)
#Ovary	(49)	(48)	(49)
Follicular cyst, NOS	11 (22%)	14 (29%)	15 (31%)
Parovarian cyst	7 (14%)	7 (15%)	3 (6%)
Hemorrhagic cyst	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, active chronic			1 (2%)
Inflammation chronic suppurative			1 (2%)
Atrophy, senile	10 (20%)	2 (4%)	2 (4%)
#Ovary/follicle	(49)	(48)	(49)
Multiple cysts	5 (10%)		
Hemorrhagic cyst		2 (4%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(48)	(46)
Inflammation, chronic focal			1 (2%)
#Cerebrum	(50)	(48)	(46)
Atrophy, pressure	1 (2%)		2 (4%)
#Cerebellar white matter	(50)	(48)	(46)
Cytoplasmic vacuolization			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic focal		2 (4%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract		2 (4%)	
Harderian gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 1,4-DICHLOROBENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)	
Osteosclerosis	1 (2%)		1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS	2 (4%)	2 (4%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic	1 (2%)	2 (4%)	1 (2%)
*Peritoneum	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Peritoneal mesothelium	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
*Epicardium	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation necro granulomatous			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF 1,4-DICHLOROBENZENE

TABLE E1. MUTAGENICITY OF 1,4-DICHLOROBENZENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	134 ± 9.2	171 ± 2.1	212 ± 11.4
	1.0	144 ± 8.8	180 ± 13.5	202 ± 7.9
	3.3	153 ± 4.5	179 ± 15.7	196 ± 2.1
	10.0	152 ± 5.0	185 ± 31.1	211 ± 8.5
	33.0	145 ± 11.4	172 ± 15.2	189 ± 7.5
	100.0	108 ± 9.0	141 ± 18.7	164 ± 8.6
TA1535	0.0	4 ± 1.8	9 ± 0.3	6 ± 1.5
	1.0	4 ± 0.3	8 ± 1.0	6 ± 0.7
	3.3	5 ± 0.9	10 ± 0.9	8 ± 2.9
	10.0	4 ± 0.7	11 ± 1.7	8 ± 2.6
	33.0	7 ± 1.5	10 ± 1.7	6 ± 1.0
	100.0	4 ± 0.9	7 ± 1.5	5 ± 1.9
TA1537	0.0	9 ± 1.8	13 ± 3.8	18 ± 0.9
	1.0	7 ± 1.2	12 ± 1.2	16 ± 4.2
	3.3	8 ± 0.9	13 ± 2.6	14 ± 0.0
	10.0	8 ± 0.3	10 ± 1.0	16 ± 2.6
	33.0	9 ± 3.2	10 ± 1.0	13 ± 2.3
	100.0	9 ± 0.7	11 ± 0.6	17 ± 1.2
TA98	0.0	13 ± 1.5	15 ± 1.5	18 ± 2.0
	1.0	12 ± 1.2	17 ± 2.9	20 ± 2.0
	3.3	14 ± 0.9	18 ± 4.5	14 ± 3.5
	10.0	14 ± 2.3	18 ± 2.1	20 ± 2.0
	33.0	11 ± 2.6	19 ± 1.2	20 ± 1.9
	100.0	9 ± 1.7	19 ± 2.4	22 ± 1.9

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE E2. MUTAGENICITY OF 1,4-DICHLOROBENZENE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (µg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO (1%)		113	88.2	100.4	43
		77	88.2	101.2	29
		73	74.7	96.4	33
		90	79.3	102.0	38
Methyl methane sulfonate					
	15	236	24.8	29.3	317
		315	25.8	22.8	406
1,4-Dichlorobenzene					
	65	86	73.0	81.4	39
		66	66.7	77.2	33
	85	123	86.7	49.3	47
		83	73.3	47.1	38
	95	144	76.0	16.1	63
		109	85.8	15.2	42

(a) Experiments were performed twice; all doses were tested in duplicate or triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). 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 supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE E3. MUTAGENICITY OF 1,4-DICHLOROBENZENE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9 (a)

Compound		Dose (µg/ml)	Total Mutant Clones	Relative Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO (1%)	A.		159	76.2	120.8	70
			148	91.0	87.8	54
			167	66.8	86.3	83
			154	72.5	105.1	71
	B.		67	63.0	98.1	35
			67	85.5	117.5	26
			73	68.0	88.4	36
			86	70.3	95.9	41
	C.		166	79.7	100.0	69
			161	67.0	102.9	80
			175	81.2	100.0	72
			188	87.5	97.1	72
3-Methylcholanthrene	A.	2.5	598	66.5	64.3	300
			561	65.5	49.9	285
	B.		498	48.3	32.8	343
			466	40.5	32.6	384
	C.		627	51.7	43.7	405
			652	70.7	64.4	308
1,4-Dichlorobenzene	A.	70	187	79.8	60.8	78
			129	58.0	46.0	74
		80	136	46.0	38.5	99
			177	61.2	37.6	96
		90	115	46.5	20.9	82
			147	54.0	20.9	91
		100	147	58.5	18.1	84
			218	79.3	21.2	92
	B.	65	112	58.2	34.6	64
			78	54.5	38.5	48
		85	83	69.5	23.5	40
			92	73.2	21.0	42
		95	155	49.8	10.0	104
			140	64.2	11.6	73
	C.	80	188	69.0	46.1	91
			211	69.0	42.0	102
		85	247	73.2	26.6	113
			214	68.7	26.2	104
		90	306	91.5	25.6	111
			175	94.7	36.8	62
		95	241	87.3	27.2	92
			217	66.7	19.1	108
		100	245	77.0	17.3	106
			229	57.5	18.8	133

(a) Experiments were performed twice; all doses were tested in duplicate. Three separate experiments were performed (A, B, and C). The protocol was basically that of Clive et al. (1979). 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 supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the liver of Aroclor 1254-induced male F344 rats.

TABLE E4. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 1,4-DICHLOROBENZENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell (d)	Dose (µg/ml)	SCE/Cell (d)
DMSO (10 µl)	8.1	DMSO (10 µl)	8.2
1,4-Dichlorobenzene		1,4-Dichlorobenzene	
75	8.8		
100	7.8	100	7.7
125	8.4	125	8.8
150	8.6	150	7.2
Mitomycin C		Cyclophosphamide	
0.005	24.8	1.5	29.9

(a) SCE = sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 µM BrdU was added, and incubation was continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 µM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE E5. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 1,4-DICHLOROBENZENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells with abs)	Dose (µg/ml)	Abs/100 Cells (percent cells with abs)
DMSO (10 µl)	2 (2)	DMSO (10 µl)	4 (3)
1,4-Dichlorobenzene		1,4-Dichlorobenzene	
50	1 (1)	25	6 (6)
100	2 (2)	50	2 (2)
150	7 (5)	100	5 (3)
Mitomycin C		Cyclophosphamide	
0.50	34 (18)	25	28 (22)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

TABLE E6. NUMBER OF MICRONUCLEATED CELLS PER THOUSAND ERYTHROCYTES IN THE FIRST THIRTEEN-WEEK STUDIES OF 1,4-DICHLOROBENZENE (a)

Dose (mg/kg)	Micronucleated Cells per 1,000 Erythrocytes ± Standard Error	No. of Mice
MALE		
0	1.16 ± 0.11	9
600	0.92 ± 0.11	10
900	1.12 ± 0.11	10
1,000	0.72 ± 0.13	10
1,500	1.51 ± 0.23	6
1,800	1.32 ± 0.20	3
FEMALE		
0	0.82 ± 0.11	10
1,200	0.75 ± 0.10	10
1,500	0.91 ± 0.08	5
1,800	0.66	1

(a) The protocol followed was essentially that of MacGregor et al. (1980). Smears were prepared from peripheral blood samples of dosed animals. Slides were air dried, fixed in absolute ethanol, and stained. At least 10,000 erythrocytes were counted from each animal.

APPENDIX F

CHEMICAL CHARACTERIZATION OF 1,4-DICHLOROBENZENE

APPENDIX F. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of 1,4-Dichlorobenzene Lot No. D4577 Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Physical properties		
1. Melting point:	49°-55.1° C (visual capillary) Major endotherm at 57.5°-58° C; very slight endotherm at 49°-51° C (Dupont 900 DTA)	53.5° C (Merck Index, 1976)
2. Appearance:	White crystals	
B. Spectral data		
1. Infrared		
Instrument:	Beckman IR-12	
Cell:	Melt between sodium chloride plates	
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Petroleum ether	

Results:

λ_{max} (nm)	ε_{max}	λ_{max} (nm)	ε_{max}
281.7	470.4 ± 8.5	282	504
273.4	535.8 ± 11.7	273	588
267.9	318.0 ± 7.1	268 (shoulder)	353
265.6	367.2 ± 8.2	266	397
260.5	221.9 ± 5.2	260	242
258.7	218.6 ± 5.4	258 (shoulder)	235
253.5	135.7 ± 2.8	253 (shoulder)	147
252.0	125.8 ± 2.4	252 (shoulder)	140
228.0	10,404 ± 133	229	13,819
224.5	12,539 ± 158	224.5	16,759
No absorbances between 350 and 800 nm		(Calculated from literature spectrum; Sadtler Standard Spectra)	

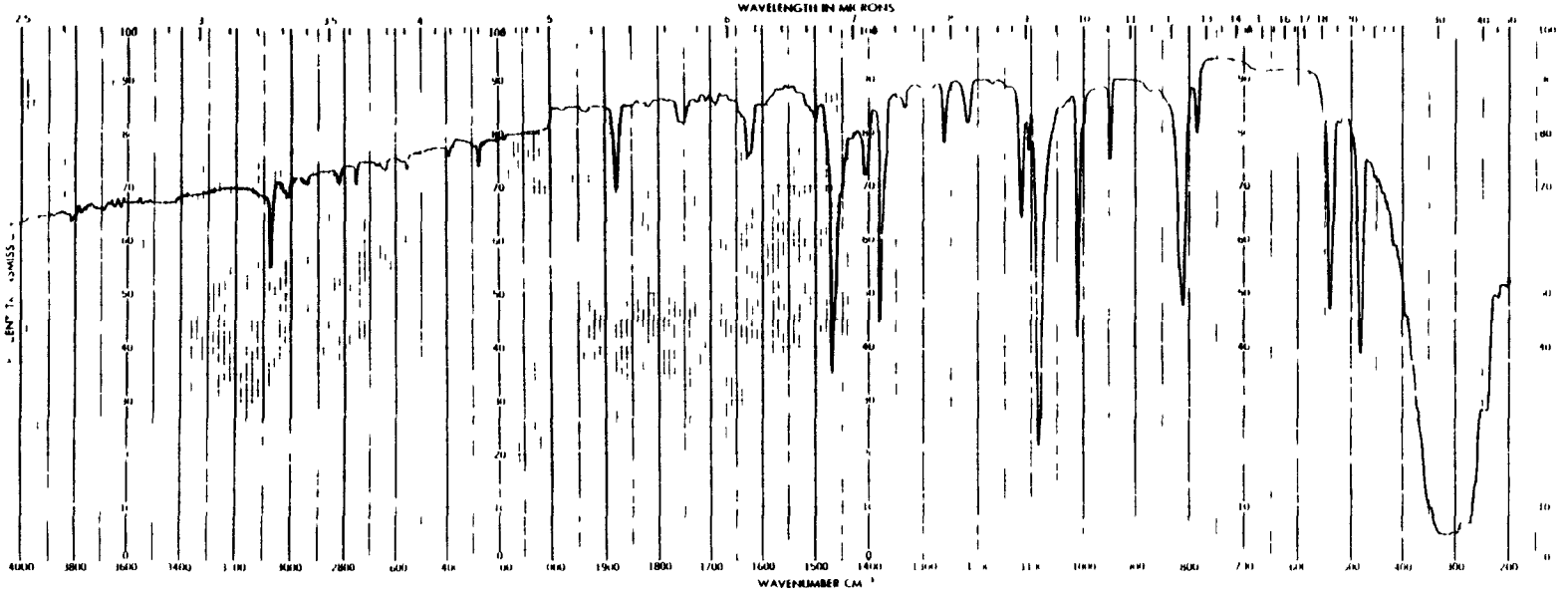

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF 1,4-DICHLOROBENZENE (LOT NO. D4577)

	Determined	Literature Values
3. Nuclear magnetic resonance		
Instrument:	Varian HA-100	
Solvent:	Deuterated chloroform	
Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	a 7.06 ppm	
Integration ratios:	a 4.00	

C. Water analysis (Karl Fischer): 0.297% ± 0.073(δ)%

D. Elemental analysis

Element	C	H	Cl
Theory	49.02	2.74	48.24
Determined	48.97	2.66	48.09
	48.75	2.74	48.28

E. Gas chromatography

System 1

Instrument: Tracor MT 220
Detector: Flame ionization
Column: 3% SP2250 on 80/100 Supelcoport, 1.7 m × 4 mm ID, glass
Inlet temperature: 220° C
Detector temperature: 260° C
Carrier gas: Nitrogen, 70 ml/min
Oven temperature program: 5 min at 70° C, then 70° C to 250° C at 10° C/min
Sample injected: (5.0 µl) 1% in hexane, and 0.1% and 0.05% in hexane to check for overloading and quantitate major peak

Results: Single homogenous peak. No attempt was made to look for or quantitate impurities <0.01% (100 ppm) of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	4.25	1.00	100

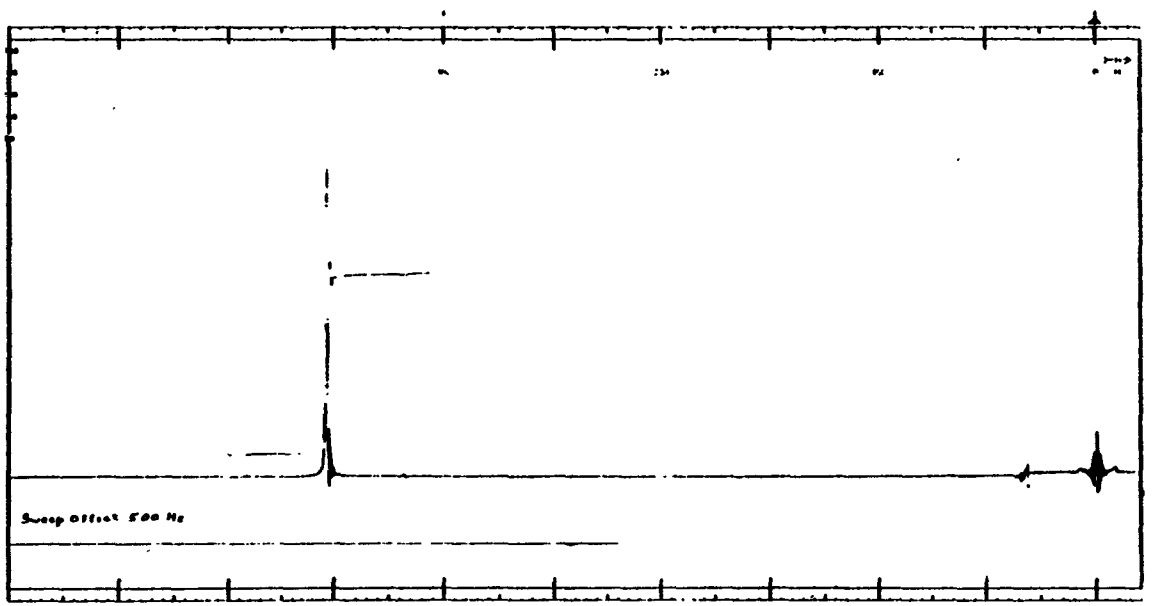

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 1,4-DICHLOROBENZENE (LOT NO. D4577)

System 2

Instrument: Varian Aerograph 2400
Detector: Flame ionization
Column: 3% OV 225 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 210° C
Detector temperature: 270° C
Carrier gas: Nitrogen, 50 ml/min
Oven temperature program: 5 min at 50° C, then 50° C to 250° C at 10° C/min
Sample injected: (8 µl) 10% in hexane, and 1.0% and 0.5% in hexane to check for overloading and quantitate the major peak

Results: Single homogenous peak. No attempt was made to look for or quantitate impurities <0.01% (100 ppm) of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	7.1	1.00	100

F. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, and chlorine were in agreement with the theoretical values. Two gas chromatographic systems indicated no impurities with areas 0.01% or greater of the area of the major peak. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with the literature spectra.

II. Analysis for the Presence of the 1,2- and 1,3- Isomers of Dichlorobenzene

A. System

Instrument: Varian 3700
Detector: Flame ionization
Column: 3% SP2250 on 100/120 Supelcoport, 1.8 m × 2 mm ID, glass
Inlet temperature: 170° C
Detector temperature: 250° C
Carrier gas: Helium, 30 ml /min
Oven temperature: 40° C, isothermal

B. Results: Separate standard solutions of 1,2- and 1,3-dichlorobenzene (1.5 µl of 0.013 mg/ml in methylene chloride), when injected on the system described above, had retention times of 20.55 and 14.80 minutes, respectively. Injection of 1,4-dichlorobenzene (1.5 µl of a 10 mg/ml solution in methylene chloride) did not reveal any peaks with retention times corresponding to either isomer. From peak heights obtained from quantitative spikes, it was estimated that concentrations as low as 0.03%-0.05% (w/w) of either isomer could be detected in the sample.

III. Chemical Stability Study of 1,4-Dichlorobenzene Lot No. D4577 Performed by the Analytical Chemistry Laboratory

A. Storage: Samples of 1,4-dichlorobenzene were stored at −20°, 5°, 25°, or 60° C for 2 weeks in glass screw-capped tubes with Teflon®-lined caps.

B. Analytical method: Duplicate aliquots (approximately 100 mg) of each of the above samples were accurately weighed into glass-stoppered flasks, and petroleum ether (10.0 ml) containing 1% *n*-decane was added. These solutions were analyzed by the gas chromatographic system described below.

Instrument: Varian Aerograph 2400 Series with Hewlett-Packard 3380A automatic recorder/integrator
Detector: Flame ionization
Column: 0.3% SP2250 on 80/100 Supelcoport, 1.8 × 4 mm ID, glass
Inlet temperature: 150° C
Detector temperature: 200° C
Oven temperature program: 100° C, isothermal
Retention times: 1,4-dichlorobenzene--4.5 min; *n*-decane--2.5 min (internal standard)

C. Results: The area of the 1,4-dichlorobenzene peak was compared with the area of the *n*-decane peak in the same injection. These areas, adjusted for the weight of the sample, were then compared with the area of the 1,4-dichlorobenzene in the sample stored at −20° C.

Storage Temperature	Percent of 1,4-Dichlorobenzene
−20° C	100.0 ± 2.0
5° C	101.0 ± 3.2
25° C	99.4 ± 1.1
60° C	97.7 ± 0.7

D. Conclusions: 1,4-Dichlorobenzene is stable when stored for 2 weeks at temperatures up to 60° C.

IV. Chemical Stability Study of Lot No. D4577 Performed by the Study Laboratory

A. Storage conditions

Bulk: Room temperature
Reference: −20° C in screw-cap glass vials

B. Analytical methods

1. Infrared spectroscopy

Instrument: Digilab FTS-10 (Fourier Transform IR System) or FTS-14 ; samples run in potassium bromide pellet

2. **Gas chromatography**

Instrument: Hewlett-Packard 5840A gas chromatograph with data terminal or Varian Aerograph 2100 gas chromatograph with CDS 111L Data System
Column: 3% OV-1, 2 m × 2 mm ID, glass
Detector temperature: 230° C
Injector temperature: 170° C
Temperature program: 50° C for 4 min, then 50° C to 250° C at 10° C/min
Carrier: Nitrogen, 20-40 ml/min
Sample size: 2 µl
Concentration: 1.0% and 0.5% in chloroform

C. **Results**

1. **Infrared spectroscopy:** All bulk spectra were comparable to the reference spectra and to the spectrum supplied by the analytical chemistry laboratory.

2. **Gas chromatography**

	Percent Purity	
Date	Reference	Bulk
03/28/78	100	100
08/08/78	100	100
01/19/79	99.35	99.30
05/16/79	99.58	99.57
09/26/79	100	100
01/31/80	100	100
08/04/80	100	100
01/27/81	100	100
05/29/81	100	100
09/05/81	100	100
09/08/81	100	100
01/14/82	100	100
05/21/82	100	100

D. **Conclusion:** No notable degradation occurred during the studies.

APPENDIX G

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Studies Conducted at the Analytical Chemistry Laboratory

Sample preparation and storage: 1,4-Dichlorobenzene (7.9871 g) was dissolved in a 100-ml volumetric flask and diluted to volume (100 ml) with corn oil. The flask was agitated manually for 30 seconds. Aliquots (1.84 ml) of this solution were pipetted into 8.5-ml septum vials. The vials were then sealed and stored at room temperature in duplicate for up to 7 days. No attempt was made to protect the samples from light.

Sample extraction and analysis: At the end of the storage time period, methanol (2 ml) was added to each sample vial. The samples were agitated on a Vortex mixer for 1 minute and then placed in an ultrasonic vibrator bath for 2 minutes. Aliquots for analysis were removed directly from the methanol (top) layer of each sample by microliter syringe and analyzed by the gas chromatographic system described below.

Instrument: Varian 2400 with Heath chart/recorder
Detection: Flame ionization
Column: 3% OV-225 on 80/100 mesh Supelcoport, 1.8 m × 2 mm ID, glass
Temperatures
Inlet, 130° C
Oven, 75° C, isothermal
Detector, 180° C
Carrier gas: Nitrogen, 50 ml/min
Sample injected: 5 µl

Quality control protocols: Each analysis was performed in duplicate. Recovery studies were performed twice during the 7-day study (duplicate analyses at the 8%, w/v level). Linearity studies were done at three concentrations.

Results

Day	Target Percent Weight/Volume	Determined Percent Weight/Volume	Corrected Percent (a) Weight/Volume
0	8.01	2.48 ± 0.02	8.05 ± 0.06
2	7.99	2.40 ± 0.08	7.79 ± 0.26
4	7.99	2.49 ± 0.04	8.08 ± 0.12
7	7.99	2.41 ± 0.04	7.82 ± 0.12

(a) Corrected for recovery of 30.8% ± 0.4%.

Conclusion: 1,4-Dichlorobenzene mixed with corn oil at the 8% (w/v) concentration is stable when stored at room temperature for 7 days.

APPENDIX H

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX H. METHODS OF ANALYSIS

I. Study Laboratory

Procedure: Standards were prepared by serial dilution at 240, 120, 60, and 30 mg/kg. Then 1-ml aliquots of standards and samples were each placed in 9 ml of methanol, vortexed, and centrifuged for 5 minutes. The top 5-ml portion of sample was taken for analysis. Concentrations were determined from the linear regression standard curve, and analyses were done in duplicate.

Instrument: Varian Aerograph 2100 gas chromatograph with CDS 111L data system; Hewlett-Packard 5840A gas chromatograph with Hewlett-Packard data system (for dose mixtures prepared 1/14/82 and 3/11/82)
Column: 3% OV-1
Detector temperature: 180°C
Injector temperature: 130°C
Temperature program: 80°C, isothermal
Flow rate: 15 or 40 ml/min
Sample size: 1 µl

II. Analytical Chemistry Laboratory

A. **Preparation of standard spiked corn oil:** Two working standard solutions of 1,4-dichlorobenzene in methanol were prepared independently. These solutions were diluted with methanol to make four additional concentrations. Aliquots (10 or 20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 1 or 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified concentration range of the referee sample. One 35-ml septum vial containing 1 or 2 g of undosed corn oil was treated with 10 or 20 ml of methanol for use as a blank. The spiked corn oil samples and the corn oil blank were extracted immediately and analyzed by the procedure below.

B. **Preparation of referee sample:** Three separate portions (approximately 1 or 2 g each) of the referee corn oil sample were transferred to individually tared 35-ml septum vials and were weighed to the nearest 0.001 g. Methanol (10 or 20 ml) was pipetted into each vial, and then the referee samples were extracted immediately and analyzed.

C. **Analysis procedure:** The vials were sealed, vigorously agitated for 10 seconds on a vortex mixer, and then shaken for 20 minutes at maximum stroke on a Burrell Model 75 Wrist-Action® shaker. After the extraction mixtures were agitated for 3 minutes, an aliquot of the upper methanol layer from each vial was combined with an aliquot of internal standard solution (*n*-decane or *n*-undecane in methanol) and diluted with methanol. The solutions were thoroughly mixed; the 1,4-dichlorobenzene content of each solution was then determined by the gas chromatographic system described below.

The total amount of 1,4-dichlorobenzene in the referee corn oil samples was determined with a linear regression equation calculated from the standard curve relating the ratio of the peak area of the internal standard to the amount of chemical in the respective spiked corn oil sample.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 3% OV-225 on 80/100 mesh Supelcoport, 1.8 m × 4 mm ID, glass, silanized
Detection: Flame ionization
Detector temperature: 250° C
Inlet temperature: 200° C
Temperature program: 60°-80° C, isothermal or programmed
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 1 or 3 µl

D. **Quality assurance measures:** The referee oil sample was analyzed in triplicate, and the corn oil blank sample was analyzed once. Individually spiked portions of undosed corn oil (six concentrations) prepared from two independently weighed standards were used to obtain standard curve data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

APPENDIX I

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE I1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Date Mixed	Concentration (a) of 1,4-Dichlorobenzene in Corn Oil for Target Concentration (mg/ml)		
	30	60	120
06/13/80	31.6	58.6	124.0
08/05/80	31.6	62.2	113.2
10/08/80	30.5	61.0	123.0
11/19/80	32.4	61.2	119.0
01/28/81	30.1	56.9	123.3
03/18/81	30.0	62.4	127.0
05/20/81	30.4	58.4	119.0
07/22/81	31.0	61.4	127.2
09/02/81	28.4	56.0	110.4
11/16/81	31.3	61.4	126.2
01/14/82	31.1	60.4	117.1
03/11/82	29.8	56.4	124.0
Mean (mg/ml)	30.7	59.7	121.1
Standard deviation	1.05	2.32	5.44
Coefficient of variation (percent)	3.4	3.9	4.5
Range (mg/ml)	28.4-32.4	56.0-62.4	110.4-127.2
Number of samples	12	12	12

(a) Results of duplicate analysis

TABLE I2. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
06/13/80	60	58.6	62.05
11/19/80	30	32.4	30.26
11/16/81	120	126.2	118.1
03/11/82	120	124.0	118.8

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

APPENDIX J

METHODS OF CLINICAL CHEMICAL ANALYSIS

Alkaline Phosphatase analyses were performed on a Gemsaec Centrifugal Analyzer with Spin Chem® reagents. Phosphatase activity at pH 10.2 was determined by kinetic measurement of the conversion of *p*-nitrophenyl phosphate to *p*-nitrophenol (Wilkinson et al., 1969).

Serum Glutamic Pyruvic Transaminase (SGPT) activity was determined on a Gemsaec Centrifugal Analyzer with Worthington Statzyme® reagents. The procedure is based on the method of Henry et al. (1960) in which SGPT catalyzes the conversion of L-alanine to pyruvate. Pyruvate is then converted to lactate by an excess of lactate dehydrogenase in the reagent. This latter reaction is accompanied by the conversion of NADH to NAD. The formation of NAD is proportional to SGPT activity and can be measured as a decreased absorption at 340 nm.

Gamma-Glutamyl Transpeptidase (GGTP) assays were performed on a Gemsaec Centrifugal Analyzer with Worthington Statzyme® reagents. The procedure is based on the method of Szasz (1969) in which GGTP catalyzes the conversion of *gamma*-glutamyl-*p*-nitroanilide to *p*-nitroaniline, which absorbs at 405 nm. Enzyme activity is proportional to the rate of increased absorbance at this wavelength.

Bilirubin was determined on a Gemsaec Centrifugal Analyzer according to a modification of the method of Malloy and Evelyn (1937). Bilirubin reacts with diazotized sulfonilic acid to form the chromagen azobilirubin, which absorbs light at 560 nm.

Cholesterol was determined by the method of Wybenga et al. (1970) with reagent commercially prepared by Dow Diagnostics (Diagnostest® Cholesterol Reagent). By this procedure, cholesterol reacts with the reagent that is composed of ethyl acetate, sulfuric acid, and ferric perchlorate, to form a purple chromophore that is measured spectrophotometrically at 595 nm.

Triglyceride was determined enzymatically according to the method of Pinter et al. (1967) as modified by Bucolo and David (1973).

Urea Nitrogen (BUN) was determined with diacetylmonixine thiosemicarbazide reagent (Wybenga et al., 1971). Color development, which is proportional to the amount of urea in the serum, was measured on a Coleman Jr. II spectrophotometer.

Glucose was determined by a hexokinase method (Barthelmai and Czok, 1962) on a Gemsaec Centrifuge Analyzer. Spin Chem® Reagent (Smith Kline, Inc.) was used for the analyses.

Total Protein was determined by the biuret color reaction (Weichselbaum, 1946) on a Gemsaec Centrifugal Analyzer.

Globulin was determined by the glyoxylic acid reaction (Hopkins and Cole, 1901) as modified by Goldenberg and Drews (1971). Reagents were obtained from Dow Diagnostics. Color development was measured on a Coleman Jr. II spectrophotometer.

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. 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 are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 7, 11, and 19 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are 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)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus)	RCV (rat coronavirus) Sendai	

II. Results

TABLE K1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
Rats	7	--	None positive
	11	--	None positive
	19	--	None positive
	24	1/10	KRV
Mice	7	--	None positive
	11	--	None positive
	19	1/9	LCM
	24	1/10	Reo 3
		5/10	MHV

(a) Blood samples were taken from sentinel animals at 7, 11, and 19 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX L

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

Pelleted Diet: March 1980 to April 1982

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

TABLE L1. 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
Brewer's dried 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 L2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
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 L3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	No. of Samples
Crude protein (percent by weight)	24.14 ± 0.88	22.7-25.1	24
Crude fat (percent by weight)	4.77 ± 0.34	4.1-5.4	24
Crude fiber (percent by weight)	3.31 ± 0.50	1.4-4.3	24
Ash (percent by weight)	6.67 ± 0.49	5.83-7.43	24
Vitamins			
Vitamin A (IU/kg)	10,700 ± 2,350	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.4 ± 4.5	7.3-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.32 ± 0.20	0.81-1.69	24
Phosphorus (percent)	1.01 ± 0.08	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) was not analyzed for thiamine.

TABLE L4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	No. of Samples
Arsenic (ppm)	0.38 ± 0.23	<0.05-1.06	24
Cadmium (ppm) (a)	<0.11 ± 0.07	<0.01-0.40	24
Lead (ppm)	0.91 ± 0.51	0.50-2.65	24
Mercury (ppm) (b)	< 0.05		24
Selenium (ppm)	0.30 ± 0.09	0.10-0.52	24
Aflatoxins (ppb) (b,c)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (d,e)	7.17 ± 3.66	<0.1-13.0	24
Nitrite nitrogen (ppm) (d,e)	1.88 ± 1.58	<0.1-6.9	24
BHA (ppm) (f,g)	4.39 ± 3.72	<0.4-13.0	24
BHT (ppm) (f)	2.67 ± 1.50	0.8-5.9	24
Aerobic plate count (CFU/g)	45,008 ± 33,225	5,500-120,000	24
Coliform (MPN/g) (h)	36.4 ± 5	<3-240	23
Coliform (MPN/g) (i)	125 ± 3	<3-1,100	
E. coli (MPN/g) (j)	<3		24
Total nitrosamines (ppb) (k,l)	7.16 ± 6.92	0.8-24.5	21
Total nitrosamines (ppb) (k,m)	29.36 ± 64.76	0.8-273	24
N-Nitrosodimethylamine (ppb) (k,l)	5.54 ± 6.03	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (k,m)	27.55 ± 64.41	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.34 ± 0.93	0-3.5	24
Pesticides (ppm)			
α-BHC (n)	<0.01		24
β-BHC (b)	<0.02		24
γ-BHC-Lindane (b)	<0.01		24
δ-BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (b,o)	<0.01	0.09 (8/26/81)	24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (b)	<0.05		24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCBs (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (o)	<0.1	0.2 (4/27/81)	24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (p)	0.09 ± 0.07	<0.05-0.27	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

TABLE L4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Two batches contained more than 0.1 ppm.
(b) All values less than detection limit, given in table as the mean
(c) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(d) Source of contamination--alfalfa, grains, and fish meal
(e) Two batches contained less than 0.1 ppm.
(f) Source of contamination--soy oil and fish meal
(g) Three batches contained less than 0.5 ppm.
(h) Excludes one very high value of 1,100 obtained for the batch produced on 12/16/80; MPN = most probable number.
(i) Includes the high value listed in footnote (h)
(j) All values were <3 MPN/g.
(k) All values are corrected for percent recovery.
(l) Mean, standard deviation, and range exclude three very high values in the range of 115-280 ppb for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote (l).
(n) BHC is hexachlorocyclohexane or benzene hexachloride.
(o) One value above the detection limit (noted in the range column) was obtained on this date.
(p) Twelve batches contained more than 0.05 ppm.

APPENDIX M

RESULTS OF SUPPLEMENTARY ANALYSES PERFORMED DURING THE FIRST THIRTEEN-WEEK STUDIES

TABLE M1. ANALYSIS OF ORGAN WEIGHT TO BRAIN WEIGHT RATIOS FOR RATS IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a,b)

	Vehicle Control	300 mg/kg	600 mg/kg	900 mg/kg	1,200 mg/kg	1,500 mg/kg
MALE						
No. examined	9	10	10	9	5	2
Organ						
Brain (c)	1,832 ± 26.8	1,766 ± 22.2	1,765 ± 23.8	1,777 ± 16.3	1,810 ± 36.1	1,710 ± 110.5
Heart	4.99 ± 0.187	5.01 ± 0.223	5.22 ± 0.196	4.99 ± 0.311	4.58 ± 0.221	4.29 ± 0.336
Kidney	5.43 ± 0.092	5.71 ± 0.137	(d) 5.89 ± 0.120	(e) 6.22 ± 0.209	(d) 6.00 ± 0.231	5.79 ± 0.023
Liver	51.10 ± 0.980	48.90 ± 1.810	54.90 ± 1.530	(e) 61.00 ± 2.220	(e) 60.50 ± 2.520	(d) 56.30 ± 4.170
Lung	8.16 ± 0.436	8.25 ± 0.276	7.68 ± 0.350	8.41 ± 0.456	7.57 ± 0.730	6.97 ± 0.339
Spleen	3.27 ± 0.078	3.32 ± 0.137	3.08 ± 0.085	3.29 ± 0.089	2.98 ± 0.163	2.76 ± 0.260
Testis	12.60 ± 1.420	12.40 ± 0.750	12.30 ± 0.610	11.60 ± 0.370	11.70 ± 0.650	11.00 ± 0.240
Thymus	1.83 ± 0.144	1.64 ± 0.125	1.72 ± 0.131	1.43 ± 0.101	1.51 ± 0.160	(e) 0.97 ± 0.151
FEMALE						
No. examined	10	10	10	8	9	1
Organ						
Brain (c)	1,662 ± 26.6	1,641 ± 34.0	1,653 ± 16.3	1,648 ± 18.9	1,611 ± 26.7	(g)
Heart	3.57 ± 0.145	3.66 ± 0.140	3.70 ± 0.202	3.52 ± 0.104	3.72 ± 0.242	(g)
Uterus	5.13 ± 0.833	(e) 2.51 ± 0.216	(e) 2.23 ± 0.192	(e) 2.81 ± 0.396	(e) 2.45 ± 0.293	(g)
Ovary (f)	4.82 ± 0.821	3.79 ± 0.456	3.24 ± 0.199	5.03 ± 0.999	4.42 ± 0.679	(g)
Kidney	3.95 ± 0.098	4.03 ± 0.128	3.82 ± 0.064	3.90 ± 0.129	4.07 ± 0.127	(g)
Liver	30.00 ± 0.900	33.30 ± 1.220	32.40 ± 0.990	(e) 36.40 ± 1.270	(e) 38.20 ± 1.160	(g)
Lung	6.68 ± 0.267	7.70 ± 0.692	6.54 ± 0.262	5.94 ± 0.298	6.15 ± 0.299	(g)
Spleen	2.48 ± 0.079	2.47 ± 0.094	2.34 ± 0.052	2.29 ± 0.056	(e) 2.12 ± 0.098	(g)
Thymus	1.41 ± 0.071	1.46 ± 0.140	1.33 ± 0.063	1.35 ± 0.115	1.42 ± 0.084	(g)

(a) 10 × organ weight (in milligrams)/brain weight (in milligrams) ± standard error except as noted
(b) The P values in Tables M1-M4 were determined by Dunnett's test when a nonsignificant result was obtained by the Jonckheere trend test; otherwise Williams' test was used (Dunnett, 1980; Jonckheere, 1954; Williams, 1971, 1972).
(c) Absolute weight, milligrams ± standard error
(d) $P<0.05$ versus vehicle controls
(e) $P<0.01$ versus vehicle controls
(f) 100 × ratio ± standard error
(g) Statistical analysis was not performed because only one animal was examined.

TABLE M2. ANALYSIS OF ORGAN WEIGHT TO BRAIN WEIGHT RATIOS FOR MICE IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	600 mg/kg	900 mg/kg	1,000 mg/kg	1,500 mg/kg	1,800 mg/kg
MALE						
No. examined	9	10	10	9	6	3
Organ						
Brain (b)	448 ± 5.72	440 ± 7.15	442 ± 8.54	434 ± 8.01	452 ± 3.07	433 ± 6.67
Heart	3.62 ± 0.118	3.63 ± 0.137	3.48 ± 0.135	3.50 ± 0.142	3.21 ± 0.067	(c) 2.93 ± 0.107
Kidney	6.38 ± 0.096	(d) 5.70 ± 0.195	(d) 5.62 ± 0.126	5.72 ± 0.260	6.28 ± 0.282	5.54 ± 0.157
Liver	33.00 ± 0.500	33.20 ± 0.910	(c) 41.00 ± 0.910	(c) 44.30 ± 1.290	(c) 54.60 ± 3.710	(c) 57.50 ± 2.240
Lung	6.01 ± 0.678	5.20 ± 0.187	5.69 ± 0.375	5.12 ± 0.361	5.23 ± 0.455	4.85 ± 0.152
Spleen	2.33 ± 0.165	(c) 1.77 ± 0.107	(c) 1.49 ± 0.094	(c) 1.56 ± 0.100	(c) 1.47 ± 0.084	(c) 1.40 ± 0.127
Testis	5.26 ± 0.553	5.04 ± 0.181	6.12 ± 0.616	5.23 ± 0.527	5.25 ± 0.589	5.08 ± 0.207
Thymus (e)	9.81 ± 0.672	8.06 ± 0.946	9.87 ± 0.956	8.82 ± 0.730	9.43 ± 2.246	10.38 ± 0.400
FEMALE						
No. examined	10	10	10	10	5	1
Organ						
Brain (b)	454 ± 5.42	445 ± 7.03	453 ± 7.75	463 ± 7.75	450 ± 12.25	(f)
Heart	2.73 ± 0.111	2.48 ± 0.117	2.67 ± 0.116	2.53 ± 0.084	2.72 ± 0.116	(f)
Uterus	4.03 ± 0.905	3.41 ± 0.364	4.77 ± 0.700	3.51 ± 0.466	3.68 ± 1.107	(f)
Ovary (g)	4.79 ± 0.894	6.36 ± 1.014	8.48 ± 1.798	7.60 ± 1.044	(c) 11.09 ± 1.979	(f)
Kidney	3.86 ± 0.190	3.73 ± 0.078	4.02 ± 0.178	3.95 ± 0.096	(c) 4.53 ± 0.130	(f)
Liver	23.40 ± 1.180	25.50 ± 0.590	(c) 33.50 ± 1.220	(c) 30.10 ± 0.850	(c) 44.50 ± 1.010	(f)
Lung	5.17 ± 0.228	4.77 ± 0.242	4.73 ± 0.438	4.76 ± 0.200	4.54 ± 0.187	(f)
Spleen	1.53 ± 0.093	1.39 ± 0.069	1.65 ± 0.043	1.47 ± 0.067	1.47 ± 0.118	(f)
Thymus (g)	8.52 ± 0.614	9.44 ± 0.658	(d) 12.18 ± 0.811	(d) 11.19 ± 1.106	(c) 13.31 ± 2.080	(f)

(a) 10 × organ weight (in milligrams)/brain weight (in milligrams) ± standard error except as noted
(b) Absolute weight, miligrams ± standard error
(c) $P<0.01$ versus vehicle controls
(d) $P<0.05$ versus vehicle controls
(e) 100 × ratio ± standard error; n = 7 for the 1,000 mg/kg group and n = 9 for the 900 mg/kg group
(f) Statistical analysis was not performed because only one animal was examined.
(g) 100 × ratio ± standard error

TABLE M3. ANALYSIS OF HEMATOLOGY AND CLINICAL CHEMISTRY DETERMINATIONS FOR RATS IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	300 mg/kg	600 mg/kg	900 mg/kg	1,200 mg/kg	1,500 mg/kg
MALE						
No examined (b)	9	10	10	9	5	2
WBC (1,000/mm^3)	6 644 ± 0 533	6 533 ± 0 213 (9)	7 189 ± 0 281 (9)	7 012 ± 0 282 (8)	6 020 ± 0 498	7 100 ± 2 100
Lymphocytes (1,000/mm^3)	5 141 ± 0 355	5 043 ± 0 228 (9)	5 572 ± 0 251 (9)	5 176 ± 0 322 (8)	4 903 ± 0 424	5 551 ± 1 901
Segmented neutrophils (1,000/mm^3)	1 484 ± 0 360 (8)	1 413 ± 0 150 (9)	1 547 ± 0 116 (9)	1 756 ± 0 306 (8)	1 053 ± 0 105	1 290 ± 0 090
Eosinophils (1,000/mm^3)	0 134 ± 0 025 (8)	0 077 ± 0 033 (9)	0 070 ± 0 021 (9)	0 080 ± 0 023 (8)	0 064 ± 0 029	0 259 ± 0 109
Hematocrit (%)	50 1 ± 0 81	(c) 47 8 ± 0 91 (9)	(d) 47 3 ± 0 69 (9)	(c) 47 2 ± 0 40	(c) 47 6 ± 0 81	(d) 42 5 ± 0 50
Hemoglobin (g/dl)	17 6 ± 0 21	(d) 16 4 ± 0 21 (9)	(d) 16 5 ± 0 19 (9)	(d) 16 5 ± 0 16	(d) 16 6 ± 0 34	(d) 15 3 ± 0 15
MCV (cubic microns)	50 6 ± 0 69	50 0 ± 0 53 (9)	49 3 ± 0 17 (9)	(d) 48 3 ± 0 17	(d) 48 8 ± 0 37	(c) 48 0 ± 0 00
Platelets (1,000/mm^3)	365 6 ± 27 80	352 8 ± 12 70	303 3 ± 26 03	318 1 ± 24 71	399 0 ± 34 75	397 5 ± 67 50
RBC (1 000,000/mm^3)	10 0 ± 0 12	(d) 9 5 ± 0 11 (9)	(d) 9 5 ± 0 12 (9)	(d) 9 7 ± 0 09	(c) 9 8 ± 0 17	(d) 8 8 ± 0 16
Reticulocytes (%)	1 5 ± 0 21	(d) 2 8 ± 0 19	2 2 ± 0 24 (9)	(d) 3 7 ± 0 38	1 9 ± 0 26	1 9 ± 0 55
Alkaline phosphatase (IU)	163 8 ± 6 24 (8)	(d) 114 2 ± 4 56	(d) 122 4 ± 9 89	(d) 115 1 ± 12 57	(d) 121 4 ± 4 85	(e)
Cholesterol (mg/dl)	53 6 ± 4 09 (8)	58 9 ± 2 75	(d) 72 0 ± 2 40	(d) 80 2 ± 3 98	(d) 86 0 ± 3 13	(e)
Liver porphyrins (ng/g liver)	142 5 ± 15 77	146 8 ± 10 34	163 4 ± 13 78	145 9 ± 8 62	166 7 ± 23 38	113 0 ± 13 04
Glucose (mg/dl)	151 9 ± 8 58 (8)	(d) 193 8 ± 4 27	(d) 181 6 ± 4 07	167 3 ± 8 47	163 2 ± 5 43	(e)
SGPT (IU/liter)	60 2 ± 7 75 (6)	62 6 ± 14 63	41 6 ± 2 54	45 7 ± 2 88	53 0 ± 2 52 (4)	(e)
Total bilirubin (mg/dl)	0 360 ± 0 021 (7)	0 313 ± 0 019	(c) 0 251 ± 0 028	(c) 0 259 ± 0 024	0 340 ± 0 026	(e)
Total protein (g/dl)	7 1 ± 0 18 (8)	(d) 6 4 ± 0 15	(d) 6 3 ± 0 14	(c) 6 5 ± 0 10	6 9 ± 0 12	(e)
Triglyceride (mg/dl)	209 4 ± 16 88 (8)	(d) 121 1 ± 11 58	(d) 158 1 ± 13 42	(d) 86 1 ± 7 69	(d) 114 0 ± 16 26	(e)
Urinary coproporphyrin (microgram/24 h)	0 299 ± 0 045				(d) 1 83 ± 0 19	(d) 2 00 ± 1 01
Total urine (ml/24 h)	5 4 ± 0 52				7 4 ± 0 87	7 8 ± 3 80
Blood urea nitrogen (mg/dl)	22 9 ± 1 44 (8)	24 5 ± 0 75	24 0 ± 1 02	(d) 28 4 ± 1 21	(d) 28 0 ± 1 30	(e)
Urinary uroporphyrin (microgram/24 h)	0 632 ± 0 110				(c) 1 70 ± 0 35	(c) 1 92 ± 1 04
FEMALE						
No examined (b)	10	10	10	8	9	1
WBC (1,000/mm^3)	6 470 ± 0 353	6 310 ± 0 289	5 560 ± 0 308	5 987 ± 0 493	6 300 ± 0 270	(e)
Lymphocytes (1,000/mm^3)	5 119 ± 0 262	4 956 ± 0 219	4 630 ± 0 232	4 899 ± 0 481	5 372 ± 0 219	(e)
Segmented neutrophils (1,000/mm^3)	1 269 ± 0 111	1 282 ± 0 227	0 866 ± 0 112	1 026 ± 0 112	0 877 ± 0 126	(e)
Eosinophils (1,000/mm^3)	0 103 ± 0 014 (8)	0 142 ± 0 024 (5)	0 076 ± 0 011 (7)	0 100 ± 0 021 (5)	0 092 ± 0 019 (5)	(f)
Hematocrit (%)	47 7 ± 0 26	48 1 ± 0 66	47 9 ± 0 71	45 1 ± 0 40	47 3 ± 2 11	(e)
Hemoglobin (g/dl)	17 3 ± 0 11	16 9 ± 0 17	17 0 ± 0 26	16 1 ± 0 17	17 0 ± 0 72	(e)
MCV (cubic microns)	52 9 ± 0 10	52 6 ± 0 16	(d) 52 1 ± 0 10	(d) 50 5 ± 0 27	(d) 50 1 ± 0 20	(e)
Platelets (1,000/mm^3)	329 9 ± 20 08	343 0 ± 19 55	303 5 ± 22 45	311 3 ± 8 76	372 9 ± 23 97	(e)
RBC (1,000,000/mm^3)	9 0 ± 0 05	9 0 ± 0 12	9 2 ± 0 14	8 8 ± 0 10	9 3 ± 0 39	(e)
Reticulocytes (%)	2 2 ± 0 17	1 9 ± 0 16	1 7 ± 0 19	(c) 1 4 ± 0 19	2 3 ± 0 28	(e)
Alkaline phosphatase (IU)	112 4 ± 8 71	98 2 ± 10 42	100 6 ± 5 32	123 3 ± 15 59	(c) 144 1 ± 9 92	(e)
Cholesterol (mg/dl)	70 9 ± 2 52	84 0 ± 1 48	69 0 ± 2 50	(d) 88 6 ± 3 86	(d) 89 1 ± 3 35	(e)
Liver porphyrins (ng/g liver)	120 1 ± 4 18	106 5 ± 9 25	115 7 ± 6 73	113 5 ± 8 83	117 3 ± 7 24	(e)
Glucose (mg/dl)	153 8 ± 10 15	174 3 ± 6 92	170 2 ± 4 40	161 8 ± 6 80	151 4 ± 5 22	(e)
SGPT (IU/liter)	42 1 ± 3 85 (9)	50 9 ± 8 56	69 7 ± 14 08	90 3 ± 30 01	61 1 ± 7 76	(e)
Total bilirubin (mg/dl)	0 311 ± 0 045	0 262 ± 0 028	0 313 ± 0 048	0 280 ± 0 016	0 268 ± 0 022	(e)
Total protein (g/dl)	7 0 ± 0 11	7 0 ± 0 12	6 9 ± 0 13	(c) 7 4 ± 0 08	(d) 7 6 ± 0 11	(e)
Triglyceride (mg/dl)	117 1 ± 13 54	97 8 ± 6 37	118 1 ± 7 24	107 4 ± 3 36	100 7 ± 3 55	(e)
Urinary coproporphyrin (microgram/24 h)	0 189 ± 0 067 (8)				(c) 0 419 ± 0 076 (8)	(e)
Total urine (ml/24 h)	4 4 ± 0 37 (8)				5 3 ± 1 21 (8)	(e)
Blood urea nitrogen (mg/dl)	23 8 ± 1 43	23 3 ± 1 73	23 1 ± 2 11	22 1 ± 1 36	28 8 ± 2 36	(e)
Urinary uroporphyrin (microgram/24 h)	0 805 ± 0 123 (8)				1 247 ± 0 178 (8)	(e)

(a) Mean ± standard error WBC = white blood cell, MCV = mean corpuscular volume, RBC = red blood cell, SGPT = serum glutamic pyruvic transaminase
(b) If fewer animals were examined, the number is shown in parentheses following the standard error
(c) $P<0.05$ versus vehicle controls
(d) $P<0.01$ versus vehicle controls
(e) Statistical analysis not performed because only one animal was examined
(f) No animals examined

TABLE M4. ANALYSIS OF HEMATOLOGY AND CLINICAL CHEMISTRY DETERMINATIONS FOR MICE IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF 1,4-DICHLOROBENZENE (a)

	Vehicle Control	600 mg/kg	900 mg/kg	1,000 mg/kg	1,500 mg/kg	1,800 mg/kg
MALE						
No examined (b)	9	10	10	9	6	3
WBC (1,000/mm^3)	8 178 ± 0 596	(c) 4 070 ± 0 536	(d) 3 370 ± 0 495	(d) 3 812 ± 0 778 (8)	(d) 3 08 ± 0 124 (5)	(c) 3 200 ± 0 624
Lymphocytes (1,000/mm^3)	4 076 ± 0 431	3 030 ± 0 341 (9)	(c) 2 349 ± 0 251	(c) 3 182 ± 0 561 (8)	(c) 2 697 ± 0 111 (5)	2 792 ± 0 513
Segmented neutrophils (1,000/mm^3)	2 055 ± 0 548	(c) 0 635 ± 0 119 (9)	(d) 1 009 ± 0 304	(d) 0 622 ± 0 271 (8)	(d) 0 354 ± 0 042 (5)	(c) 0 369 ± 0 087
Eosinophils (1,000/mm^3)	0 046 ± 0 017	0 014 ± 0 008	0 012 ± 0 005	0 009 ± 0 009 (8)	0 030 ± 0 010 (5)	0 039 ± 0 026
Hematocrit (%)	47 33 ± 1 01	49 10 ± 0 50	46 90 ± 0 38	48 56 ± 0 82	47 33 ± 0 61	47 33 ± 0 33
Hemoglobin (g/dl)	16 00 ± 0 38	16 26 ± 0 22	15 89 ± 0 12	16 29 ± 0 34	15 58 ± 0 35	15 93 ± 0 19
MCV (cubic microns)	49 89 ± 0 65	49 10 ± 0 10	48 80 ± 0 13	49 56 ± 0 50	49 5 ± 0 81	48 67 ± 0 33
Platelets (1,000/mm^3)	691 94 ± 69 72	753 00 ± 33 73	676 25 ± 35 16	509 06 ± 37 10 (8)	635 25 ± 36 17	(d) 445 00 ± 5 00
RBC (1,000,000/mm^3)	9 47 ± 0 21	(c) 10 05 ± 0 13	9 56 ± 0 06	9 87 ± 0 21	9 57 ± 0 14	9 66 ± 0 09
Reticulocytes (%)	1 86 ± 0 30 (8)	1 34 ± 0 22	1 09 ± 0 13	1 88 ± 0 54	2 35 ± 0 36	3 27 ± 1 16
Alkaline phosphatase (IU)	33 0 ± 1 53 (6)	34 0 ± 2 59 (6)	31 8 ± 1 80 (4)	26 4 ± 1 56	40 0 ± 3 18	(d) 56 0 ± 4 00 (2)
Cholesterol (mg/dl)	91 0 ± 6 11 (3)	95 2 ± 3 31 (6)	(c) 160 0 ± 11 85 (3)	(d) 151 2 ± 9 38 (5)	(d) 179 3 ± 36 92 (3)	(d) 243 5 ± 11 50 (2)
Liver porphyrin (ng/g liver)	150 3 ± 10 91	161 8 ± 13 49	173 2 ± 15 63	(c) 214 6 ± 24 75	(d) 246 7 ± 33 2 (7)	(d) 275 4 ± 25 91
Glucose (mg/dl)	209 7 ± 14 53 (3)	256 2 ± 15 43 (5)	248 0 ± 7 64 (3)	(e)	244 0 ± 33 96 (3)	264 0 ± 23 00 (2)
SGPT (IU/liter)	63 2 ± 19 50 (5)	59 2 ± 14 62 (6)	53 7 ± 10 91 (3)	38 3 ± 3 42 (4)	43 3 ± 11 39 (4)	37 0 ± 6 00 (2)
Total bilirubin (mg/dl)	0 340 ± 0 058 (5)	0 268 ± 0 036 (6)	0 220 ± 0 064 (3)	0 256 ± 0 034 (5)	0 292 ± 0 036 (4)	0 375 ± 0 105 (2)
Total protein (g/dl)	5 67 ± 0 120 (3)	5 40 ± 0 105 (5)	5 77 ± 0 120 (3)	5 88 ± 0 189 (4)	(d) 6 63 ± 0 393 (3)	(d) 7 05 ± 0 150 (2)
Triglycerides (mg/dl)	174 3 ± 18 98 (3)	134 3 ± 5 20 (6)	176 0 ± 6 66 (3)	172 8 ± 15 27 (5)	(d) 262 0 ± 14 01 (3)	(d) 305 0 ± 28 00 (2)
Blood urea nitrogen (mg/dl)	21 0 ± 4 73 (3)	23 8 ± 1 85 (5)	22.3 ± 1 20 (3)	22 5 ± 1 50 (4)	17 0 ± 1 53 (3)	16 0 ± 2 00 (2)
FEMALE						
No examined (b)	10	10	10	10	5	1
WBC (1,000/mm^3)	3 600 ± 0 339	4 470 ± 0 371	3 450 ± 0 320	(c) 2 620 ± 0 210	(c) 2 420 ± 0 484	(e)
Lymphocytes (1,000/mm^3)	3 208 ± 0 310	4 012 ± 0 367	3 115 ± 0 314	2 375 ± 0 196	2 123 ± 0 414	(e)
Segmented neutrophils (1,000/mm^3)	0 371 ± 0 031	0 406 ± 0 061	0 335 ± 0 035	0 245 ± 0 027	0 297 ± 0 072	(e)
Hematocrit (%)	47 80 ± 0 63	48 30 ± 0 37	48 50 ± 0 22	47 50 ± 1 02	48 00 ± 0 45	(e)
Hemoglobin (g/dl)	15 95 ± 0 24	(c) 17 08 ± 0 30	16 65 ± 0 21	16 27 ± 0 38	15 98 ± 0 22	(e)
MCV (cubic microns)	48 90 ± 0 18	48 70 ± 0 21	48 50 ± 0 17	48 90 ± 0 18	49 40 ± 0 24	(e)
Platelets (1,000/mm^3)	491 95 ± 27 40	531 25 ± 31 27	(c) 649 45 ± 32 54	(c) 549 70 ± 49 78	(d) 702 40 ± 18 34	(e)
RBC (1,000,000/mm^3)	5 97 ± 0 10	6 32 ± 0 14	6 19 ± 0 07	6 03 ± 0 15	6 12 ± 0 09	(e)
Reticulocytes (%)	1 57 ± 0 25	1 34 ± 0 25	1 91 ± 0 26	1 62 ± 0 17	1 24 ± 0 11	(e)
Alkaline phosphatase (IU)	64 0 ± 6 72 (4)	82 8 ± 2 21 (6)	(c) 88 8 ± 5 65 (6)	78 4 ± 4 88 (8)	55 7 ± 1 76 (3)	(e)
Liver porphyrin (ng/g liver)	135 3 ± 15 15	197 6 ± 23 77	155 6 ± 12 55	(c) 190 1 ± 16 45	192 6 ± 35 07	(e)
SGPT (IU/liter)	101 8 ± 49 80 (4)	186 0 ± 39 26 (5)	114 8 ± 20 74 (6)	175 8 ± 32 17 (8)	52 0 ± 9 07 (3)	(e)
Total bilirubin (mg/dl)	0 515 ± 0 055 (2)	0 480 ± 0 056 (4)	0 330 ± 0 049 (3)	0 377 ± 0 033 (4)	0 360 ± 0 012 (3)	(e)

(a) Mean ± standard error WBC = white blood cell, MCV = mean corpuscular volume, RBC = red blood cell, SGPT = serum glutamic pyruvic transaminase
(b) If different, the number is shown in parentheses following the standard error
(c) P<0 05 versus vehicle controls
(d) P<0 01 versus vehicle controls
(e) Statistical analysis was not performed because only one animal was examined

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and tables of the NTP Technical Report on the toxicology and carcinogenesis studies of 1,4-dichlorobenzene in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The studies were conducted by Battelle Columbus Laboratories under a subcontract with Tracor Jitco, Inc., from May 1980 to May 1982 and were begun before the NTP's requirement for full compliance with Good Laboratory Practice standards in October 1981. The data audit was conducted from September 9, 1984, to September 20, 1984, by the following personnel from Program Resources, Inc.: W. Oller, K. Connor, J. Winegar, J. Sagartz, S. Corson, K. Pace, and C. Rafferty. The full audit report is on file at National Toxicology Program, Research Triangle Park, North Carolina.

The audit consisted of review of the data, pathology, materials, and correspondence collected during the studies. For the inlife toxicology data, 100% of the existing records on animal receipt, mortality, and environmental conditions were audited. The pathology audit included a review of 100% of Individual Animal Data Records (IADRs) for correlation between gross observations and microscopic diagnoses, for clerical errors, and for correlation between slides and tissue blocks for vehicle control and high dose groups. Ten percent of the animals were examined for unidentified lesions, correct animal identification, and verification of reported microscopic pathology. All of the available records concerning receipt and use of the study chemical, analysis of the bulk chemical by the study laboratory, and stability and characterization testing by Midwest Research Institute were examined in the chemistry review. In the review of the available analytical chemistry data, records to verify receipt, source, and analyses of corn oil were not present. The original laboratory notebooks used to record chemical analyses and calculations were not present, but facsimile notebooks constructed from original chromatograms and spectra were present and were adequate for documentation.

A review of the inlife toxicology data revealed no instances of misdosing during the course of the studies. The major problem in the studies was the high incidence of flooding of cages in both mice (118 recorded instances) and rats (74 instances). Four vehicle control male rats were drowned. There were also documented incidences of dehydration (38 for mice and 6 for rats) and starvation (9 incidences for rats) that did not result in any deaths. There were inconsistencies in records for body weights for rats and mice. Gavage-related deaths occurred in 30 out of 103 mice and 16 out of 112 rats. These gavage-related deaths occurred in all dose groups.

The pathology review revealed some unresolved discrepancies between gross observations and microscopic diagnoses in rats (all nontarget organs) and in mice (two in target organs and five in nontarget organs). Most of these potential noncorrelations were considered to be irrelevant because corresponding microscopic nonneoplastic changes frequently regarded within limits of the normal background for animals of that age were identified; the few remaining were distributed among different tissues and dose groups and were not pursued further. Three untrimmed liver masses were found in mice; there was one untrimmed skin mass in a high dose male rat. Since the liver is a target organ, a wet tissue review of all male and female mice was performed, and all untrimmed liver nodules/masses found were trimmed, embedded, sectioned, and examined by light microscopy. These lesions have been reviewed by NTP pathologists, and the updated diagnoses are included in the results presented in this Technical Report.

Overall, the audit identified no substantive problems that would lead to a decreased confidence in the studies. Although some problems and discrepancies were identified, these were adequately resolved or were determined to not affect the outcome of the studies. In conclusion, the data examined in this audit are considered adequate to meet the objectives of the studies.

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