NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 261

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLOROBENZENE

(CAS NO. 108-90-7)

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 chemically induced 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 comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLOROBENZENE

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NATIONAL TOXICOLOGY PROGRAM
Box 12233
Research Triangle Park
North Carolina 27709

October 1985

NTP TR 261
NIH Publication No. 86-2517

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.

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).

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Special Note: This Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee on February 28, 1983 [see pages 9 and 10]. Thereafter, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis Studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix P.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. The categories of evidence of carcinogenicity adopted by the NTP in June 1983 were not used to evaluate these data.

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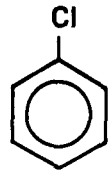

CHLOROBENZENE

CAS NO. 108-90-7

C_6H_5Cl Mol. Wt. 112.56

ABSTRACT

Toxicology and carcinogenesis studies of chlorobenzene (monochlorobenzene, >99% pure) were conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats and 50 female B6C3F$_1$ mice at doses of 60 or 120 mg/kg. Groups of 50 male B6C3F$_1$ mice received 30 or 60 mg/kg. Chlorobenzene was administered five times per week for 103 weeks. Groups of 50 rats and 50 mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls, and additional groups of 50 rats and 50 mice of each sex served as untreated controls. The chlorobenzene doses were chosen on the basis of 90-day studies, in which doses 2-fold or greater in excess of the doses used in the 2-year study caused death, hepatocellular necrosis, renal tubular injury, thymic necrosis, or lymphoid or myeloid depletion of bone marrow, spleen or thymus.

Mean body weights of dosed rats and mice were essentially the same or greater than those of the controls during the 2-year studies. Survivals of low dose male rats, dosed female rats, dosed male mice, and dosed female mice were not adversely affected by administration of chlorobenzene. Survival of high dose male rats in the 2-year study was significantly (P=0.033) lower than that of the vehicle controls. No chlorobenzene-induced toxic lesions responsible for this reduction in survival were observed. Based on the prechronic results and on the above data, the doses used in the 2-year study were considered to be adequate for carcinogenicity testing.

Male rats dosed with chlorobenzene exhibited a significant ($P<0.05$) increase in the incidence of animals with neoplastic nodules of the liver (overall incidences: untreated control, 4/50 (8%); vehicle control, 2/50 (4%); low dose, 4/49 (8%); high dose, 8/49 (16%)). Increased incidences of hepatocellular carcinomas in male rats or of neoplastic nodules or hepatocellular carcinomas in female rats were not observed. No increased tumor incidences were observed in female rats or in male or female mice.

Under the conditions of these studies, chlorobenzene administration increased the occurrence of neoplastic nodules of the liver in high dose (120 mg/kg/day) male F344/N rats, providing some but not clear evidence of carcinogenicity of chlorobenzene in male rats. Carcinogenic effects of chlorobenzene were not observed in female F344/N rats or in male or female B6C3F$_1$ mice.

CONTRIBUTORS

The carcinogenesis studies of chlorobenzene were conducted at Battelle Columbus Laboratories under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The two-year studies in rats were begun in February 1978 and completed in February 1980. The two-year studies in mice were begun in January 1978 and completed in January 1980.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLOROBENZENE

On 28 February 1983, the draft Technical Report on the toxicology and carcinogenesis studies of chlorobenzene received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Scala, a principal reviewer of the technical report on the carcinogenesis studies of chlorobenzene, agreed with the conclusion that chlorobenzene administration increased the occurrence of neoplastic nodules of the liver in male F344/N rats. He stated that the extrapolation to humans of the effects of chlorobenzene as comparable to benzene, based on structure and rodent toxicity, was speculation, and suggested that the comments in the discussion section be designated as such. Dr. W. Kluwe said that in view of the NTP findings, together with other reports indicating that some of the prechronic toxicology of chlorobenzene is similar to that of benzene, the statements as included should remain in the report. Dr. Scala agreed as long as the discussion is labeled as speculation.

As a second principal reviewer, Dr. Vore agreed with the conclusions. She found the rationale for dose selection for the long term studies both informative and well written, and thought the discussion on the metabolism of chlorobenzene was nicely done.

As a third principal reviewer, Dr. Van Ryzin agreed in general with the conclusions. He said the evidence for carcinogenic activity was not strong, being based on significant increases in neoplastic nodules in male rats at the high dose only. He stressed the decrease observed in carcinomas in male rats as well as the equivocally significant results when neoplastic nodules and carcinomas were combined. In response, Dr. Kluwe, NTP, said the final conclusion already indicates that neoplastic nodules of the liver were increased in *high dose* male rats only.

Dr. Van Ryzin questioned whether the maximum tolerated doses were achieved. He suggested that the finding of a renal tubular cell adenocarcinoma in a high dose female rat and transitional cell papillomas of the urinary bladder in a low and high dose male rat might be emphasized because of their rarity and low historical control incidence [see pages 36 and 50].

In discussion from the floor, Dr. C. R. Stack, Chlorobenzenes Program Panel of the Chemical Manufacturers Association, said her group questioned the analogy drawn between chlorobenzene toxicity and benzene toxicity. She asked that the Chlorobenzenes Program Panel have the opportunity to provide written comments on the report subsequent to the meeting. Dr. Moore said that comments would be welcomed and requested that these be received within 30 days. [None were received.]

Dr. Scala moved that the technical report on chlorobenzene be accepted with revisions discussed. Dr. Elashoff seconded the motion and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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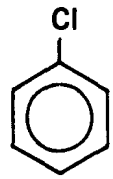

CHLOROBENZENE

CAS NO. 108-90-7

C_6H_5Cl Mol. Wt. 112.56

General

Chlorobenzene (synonyms: monochlorobenzene, chlorobenzol, phenyl chloride, benzene monochloride) is a colorless, volatile liquid under standard environmental conditions (vapor pressure = 11.8 mm Hg at 25°C, 760 mm Hg). It is used primarily as a solvent (e.g., resins, dyes, pesticides, and perfumes), a degreasing agent, and a chemical intermediate, particularly in the synthesis of nitrochlorobenzenes (Fishbein, 1979; Kirk-Othmer, 1964; NIOSH, 1981). Although still considerable, estimates of the yearly production volume of chlorobenzene in the United States indicate declining use in recent years, due to the reduced demand for organochlorine pesticides utilizing chlorobenzene as an intermediate (NIOSH, 1981; USITC, 1981).

Year	Volume of Production (Kg)
1976	170×10^6
1977	148×10^6
1978	134×10^6
1980	128×10^6 (about 142,000 tons)

The American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a threshold limit value—time weighted average (TLV-TWA) of 75 ppm (350 mg/m³; 1 ppm = 4.6 mg/m³) for chlorobenzene in air, and the Occupational Safety and Health Administration (OSHA) has similarly set the permissible exposure limit (PEL) at 75 ppm (Deichmann, 1981). Maximum recommended concentrations of chlorobenzene in air are 43 ppm in Czechoslovakia and 10 ppm in the Soviet Union (ACGIH, 1979).

Acute Effects

Oral LD_{50} values in mice, rats, rabbits, and guinea pigs were reported to be 1.44, 2.29, 2.25, and 5.06 g/kg, respectively, while an intraperitoneal LD_{50} value of 0.515 ml/kg (approximately 570 mg/kg) was reported in rats (Deichmann, 1981). Single intraperitoneal injections of chlorobenzene caused hepatocellular and renal tubular necrosis or degeneration in rats and mice (Cameron et al., 1933; Reid, 1973).

Rimington and Ziegler (1963) reported that 1140 mg/kg/day of chlorobenzene by gavage (duration of treatment unspecified) increased urinary uroporphyrin, coproporphyrin and porphobilinogen concentrations, and caused enlargement, severe necrosis and fatty degeneration of the liver. Consistent with a speculated disruption of liver heme metabolism, Ariyoshi et al. (1975) found that chlorobenzene at doses ranging from 125-1000 mg/kg/day (per os) for 3 days increased hepatic ALA-synthetase activity in rats, although hepatic microsomal protein and cytochrome P-450 concentrations were reduced.

The failure of (mono)chlorobenzene to induce hepatic microsomal drug metabolism contrasted sharply with the effects of a series of polychlorinated benzenes (*p*-dichlorobenzene, 1,3,5-trichlorobenzene, 1,2,4,5-tetrachlorobenzene, pentachlorobenzene, and hexachlorobenzene) in the studies of Ariyoshi et al. (1975). Carlson and Tardiff (1976) similarly found no increase in hepatic cytochrome P-450 concentration and no reduction in hexobarbital sleeping time in male rats receiving up to 800 mg/kg/day of chlorobenzene for 14 days, again in sharp contrast to the hepatic effects of the di-, tri- and hexachloro-

benzenes. Liver weight and hepatic UDP-glucuronyl transferase activity were increased, but hepatic glucose-6-phosphatase activity and cytochrome P-450 concentrations were decreased by the 800 mg/kg/day dose (Carlson and Tardiff, 1976). These two reports indicate major differences in biological response to the mono- and polychlorinated benzenes, specifically that monochlorobenzene is not a general inducer of hepatic microsomal drug metabolism.

Subchronic Effects

Several animal studies have shown that prolonged oral or inhalation exposures to chlorobenzene produce injury to the liver, kidney, and hematopoietic system (see Table 1). Inhalation exposures to chlorobenzene, benzene, or 1,2,4-trichlorobenzene all produced leukopenia in the study of Zub (1978), and the hematologic effects were confirmed histologically by a reported decrease in "erythro-leuko-thromboblastic cells" in the marrow of the long bones.

Another study reported "inhibitions" of erythropoiesis, thrombocytosis, and mitotic activity in bone marrow in male rats given 0.01 or 0.1 mg/kg/day chlorobenzene by gavage for 9 months (Varshavskaya, 1967). A dose of 0.001 mg/kg/day was reportedly without toxic effects.

In an unpublished study, chlorobenzene administered during organogenesis to pregnant F344 rats (days 6-15 of gestation) or New Zealand white rabbits (days 6-18 of gestation) by inhalation at 0 (control), 75, 210, or 590 ppm reportedly caused no increase in congenital malformations (Hayes et al., 1982). Because of higher than expected occurrences of unusual malformations in both control and chlorobenzene-treated litters of rabbits, an additional study was performed in this species at 0, 10, 30, 75, or 590 ppm; teratogenic effects were not observed (Hayes et al., 1982).

Metabolism

The classic studies of R.T. Williams and colleagues (Azouz et al., 1950; Parke and Williams, 1955; Smith et al., 1950) have indicated that approximately 30% of an oral dose of chlorobenzene is excreted by the lungs as unchanged compound in rabbits, and that the urinary metabolites of chlorobenzene consist of synthetic conjugates (approximately 25% glucuronides, 27% ethereal sulfates, 20% mercapturic acids), catechols (27%), and phenols (3%). The major urinary products are *p*-chlorophenylmercapturic acid and the monoglucuronide and ethereal sulfate conjugates of 4-chlorocatechol. *p*-Chlorophenol and 3,4-dihydro-3,4-dihydroxychlorobenzene were minor metabolites. *p*-Chlorophenylmercapturic acid and phenolic metabolites of chlorobenzene have been detected in the urine of rats as well (Gillham and Young, 1968).

Using ^{14}C-chlorobenzene, Smith et al. (1972) reported that rabbits excreted 20% of the administered dose in urine, 2.5% in feces, and retained 1% in the carcass (the animals were treated twice daily with 500 mg ^{14}C-chlorobenzene for 4 days, and excreta were collected during dosing and for 3 days thereafter). These authors speculated that the radioactivity not accounted for in urine, feces, and carcass, approximately 77% of the administered dose, was excreted via the lungs. The distributions of urinary metabolites in the study of Smith et al. (1972) were similar to those described in the preceding paragraph. Smith et al. (1972) speculated that the metabolites arose from the initial formation of an arene oxide intermediate, as indicated in Figure 1.

Biochemical and Subcellular Effects

Brodie and colleagues have postulated that a chemically reactive metabolite is formed *in vivo* from several aromatic organohalide compounds, including chlorobenzene, and that such a reactive intermediate could be the cause of the commonly observed liver necrosis (Brodie et al., 1971). Further studies by this group demonstrated in both rats and mice that a metabolite of chlorobenzene, possibly the arene oxide intermediate, bound irreversibly to macromolecules (e.g., proteins) in the kidney, liver, and lung (Reid, 1973; Reid et al., 1973). Since the microsomal enzyme inducer phenobarbital enhanced both binding and toxicity, while the microsomal enzyme inhibitor piperonyl butoxide reduced both of these effects, chlorobenzene appeared to be oxidized by liver enzymes to a toxic, chemically reactive product, ostensibly an arene oxide. More definitive studies have been conducted with the structurally similar chemical bromobenzene, for which it has been demonstrated that conjugation of a reactive metabolite (an arene oxide) with glutathione is a detoxification reaction (Jollow and Smith, 1977). The reactive bromobenzene metabolite appears to interact with endogenous, cellular reduced glutathione in preference to other cell macromolecules; irreversible binding to cell structures and acute liver toxicity occur only when glutathione has been substantially depleted (Jollow and Smith, 1977). Although similarities in the

TABLE 1. TOXIC EFFECTS FROM LONG-TERM EXPOSURE TO CHLOROBENZENE

Species	Dose	Duration	Effects	Reference
Rats	144 or 288 mg/kg/d; (gavage)	5d/wk x 192 d	Increased liver and kidney wts; "pathologic" liver effects	Deichmann, 1981
	376 mg/kg/d (gavage)	5d/wk x 192 d	Increased liver and kidney wts; hepatic cirrhosis, focal liver necrosis, decreased spleen wt	
Rats	250 mg/kg/d (oral)	93-99 d	Increased liver and kidney wts, no histopathological changes	Knapp et al., 1971 (abstract)
Dogs	272.5 mg/kg/d (capsule)	up to 92 d	Death in 4/8 treated dogs in 3 wks; histopathological changes in liver, kidney, gastrointestinal tract, and hematopoietic system; increase in immature circulating leukocytes	Knapp et al., 1971 (abstract)
Rats and Rabbits	75 or 250 ppm (inhalation)	7hr/d, 5d/wk x 24 wks	No deaths or changes in body wt gains, increased liver and kidney wts at 250 ppm; renal tubular regeneration in rats; transient hematologic changes in rats	NIOSH, 1977
Rats, Rabbits, Guinea Pigs	475 ppm (inhalation)	7hr/d, 5d/wk x 44 d	Liver, kidney, lung lesions, increased liver wt in guinea pigs.	Deichmann, 1981
	1,000 ppm (inhalation)	7hr/d, 5d/wk x 44 d	Liver, kidney, and lung lesions in all species	
Mice	2.5 mg/liter (544 ppm) (inhalation);	7hr/d x 3wk	Mortality, wt loss, fatty degeneration of the liver, and leukopenia.	Zub, 1978
	0.1 mg/liter (22 ppm) (inhalation)	7hr/d x 3mo	Leukopenia	

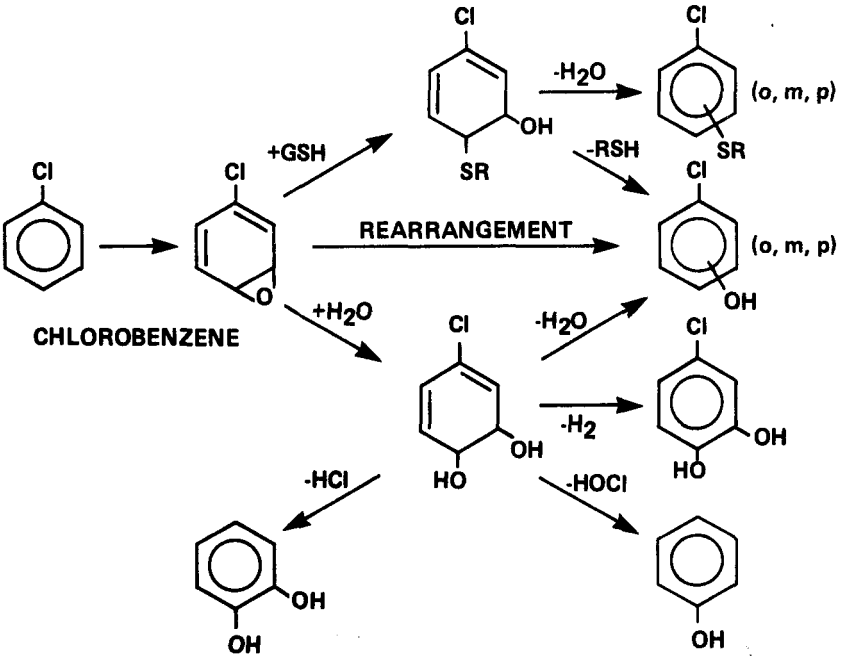

Figure 1. Metabolism of Chlorobenzene

metabolism and acute toxic effects of chloro- and bromobenzene suggest a similar relationship for chlorobenzene and hepatic glutathione, confirming studies with chlorobenzene have not been reported.

Genetic Toxicity

Additions of 0.05 or 0.1 ml of chlorobenzene to liquid suspension cultures of *Actinomycetes antibioticus*-400 were reported to cause concentration-dependent increases in the number of revertants (back-mutations; Keskinova, 1968). The chlorobenzene was identified as "pure". Lawlor et al. (1979) reported in abstract form that chlorobenzene was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538, with or without the addition of an S9 fraction from the liver of Aroclor 1254®-treated rats, and did not produce DNA damage in *E. coli* strains WP2 *uvr* A+ *rec* A+ or WP100 *uvr* A− rec A−, or *S. typhimurium* strains TA1978 *uvr* B+ or TA1538 *uvr* B−. Doses and response rates were not provided. There was also no evidence of chlorobenzene mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without metabolic activation as reported by a second group (NTP, 1982; see Appendix K). Because of the conflicting reports of mutagenic potential in bacterial systems and the lack of study in non-bacterial systems, no firm conclusion can currently be made regarding the genotoxic potential of chlorobenzene*.

Rationale for Testing

Chlorobenzene was selected for testing in the Bioassay Program because of its relatively large volume of production, the lack of prior chronic (more than 1 year of exposure in rodents) toxicity testing, and because of its detection in drinking water supplies (Dowty et al., 1975).

* The National Toxicology Program (NTP) is aware that the Chlorobenzene Producers Association, under the auspices of the Chemical Manufacturers Association, has proposed to the U.S. Environmental Protection Agency a *Voluntary Health Effects Test Program for Chlorobenzenes.* As a part of this program monochlorobenzene will be tested for potential to induce DNA repair (unscheduled DNA synthesis) and neoplastic transformation in rat liver cells *in vitro* (personal communication, Dr. C. Stack, Chemical Manufacturers Association).

II. MATERIALS AND METHODS

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TWO-YEAR STUDIES

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Data Recording and Statistical Methods

CHEMICAL ANALYSES

Chlorobenzene was obtained in a single lot (No. 77022) from Textile Chemical Company (Baltimore, MD). Purity and identity analyses were conducted at Midwest Research Institute (Appendix L). The test chemical was determined to be >99% pure based on the following: fifteen impurities with a combined area of less than 0.1% of the major peak were detected by vapor-phase chromatography, and the infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those in the literature for chlorobenzene.

Chlorobenzene was stored in the dark at room temperature at the performing laboratory (Battelle Columbus). The bulk chemical was reanalyzed periodically at Battelle Columbus Laboratories by gas chromatography and infrared spectroscopy. These analyses indicated that the test material remained stable throughout the period of storage at the laboratory.

DOSE PREPARATION

Appropriate amounts of chlorobenzene and corn oil were mixed with a stirring bar for 15 minutes in a graduated cylinder (Table 2). Chlorobenzene at a concentration of 2% (w/v) was found to be stable at 25°C for 7 days (Appendix M). Samples of chlorobenzene/corn oil mixtures were periodically analyzed at Battelle Columbus Laboratories (Appendix N). Results of these analyses and of referee analyses at Midwest Research Institute indicated that the analyzed mixtures were properly formulated.

SINGLE-DOSE STUDIES

Weanling male and female F344/N rats and hybrid B6C3F$_1$ (C57BL/6N × C3H/HeN MTV$^-$) mice were obtained from Harlan Industries and held in quarantine for 16 days before the test began. Chlorobenzene in corn oil was administered to groups of five rats and mice of each sex by gavage at doses of 250, 500, 1,000, 2,000, or 4,000 mg/kg. All animals were observed twice daily for mortality for the succeeding 14 days.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 2. Necropsies were not performed in this study.

FOURTEEN-DAY STUDIES

Weanling male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held in quarantine for 14-15 days before the study began. The animals were 6-7 weeks old when placed on study.

Groups of five rats of each sex were administered chlorobenzene in corn oil by gavage at doses of 0, 125, 250, 500, 1,000, or 2,000 mg/kg for 14 consecutive days. Groups of five mice of each sex were administered doses of 0, 30, 60, 125, 250, or 500 mg/kg in corn oil by gavage on the same schedule.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 2. The rats and mice were observed twice daily for mortality and were weighed weekly. Necropsies were performed on all animals. No microscopic analyses were performed in this study.

THIRTEEN-WEEK STUDIES

Four-week-old male and female F344/N rats and 5- to 6-week-old $B6C3F_1$ mice were obtained from Harlan Industries, observed for 2 weeks in quarantine, and then were assigned to cages according to a table of random numbers. The cages were assigned to dosed and vehicle control groups according to a second table of random numbers.

Rats and mice were housed five per cage and received water and feed *ad libitum* (Table 2). Groups of 10 rats and 10 mice of each sex were administered chlorobenzene in corn oil by gavage, 5 days per week for 13 weeks, at doses of 0, 60, 125, 250, 500, or 750 mg/kg. Animals were checked twice daily for mortality and signs of moribundity. Clinical signs were recorded daily. Individual body weight data were collected weekly. Final body weights were recorded after 13 weeks of treatment.

A 24-hour sample of urine was collected from survivors in the control and two highest dose groups during week 13 of the study. The animals were placed in polycarbonate metabolism cages (Maryland Plastics, New York) designed for separate collection of urine and feces. Food and water were provided *ad libitum*. Rats were caged singly; mice were caged in groups of 3-6. The urine was analyzed for pH, protein, glucose, ketones, bilirubin and occult blood with reagent strips (Bililabstix, Ames Corp., Elkhart, IN). Urinary specific gravity was measured with a refractometer and creatinine concentration by spectrophotometric methods. Uroporphyrins and coproporphyrins in the urine were measured by the procedure described in Appendix O.

All animals were killed during a 2-day period following the 13 weeks of treatment. Blood samples were collected from the orbital venous plexus the day before death, and analyzed for hemoglobin content, packed cell volume, total and differential white blood cell count, red blood cell count, mean corpuscular volume, platelet count and reticulocyte count. Another sample of blood was collected by cardiac puncture at sacrifice and analyzed for alkaline phosphatase, glutamic pyruvic transaminase and gamma-glutamyl transpeptidase activities, and for bilirubin, cholesterol, triglyceride, urea nitrogen (BUN), total protein and globulin contents. Terminal body weights were recorded at sacrifice, after exsanguination. Lung, liver, heart, spleen, thymus, brain, kidney (right), and testis (right), or ovary (right) and uterus were removed and weighed. Organ weight to terminal body weight ratios were calculated.

Total porphyrin contents in liver samples collected at necropsy were measured according to the methods described in Appendix O.

The following tissues were examined histologically from control, 500, and 750 mg/kg groups of rats and from control, 250, 500, and 750 mg/kg groups of mice: gross lesions, skin, mandibular or mesenteric lymph nodes, mammary gland, salivary gland, vertebrae with marrow, femur, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, small intestine, colon, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, prostate/testes or ovaries/uterus, brain, and pituitary. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Other histologic examinations were limited to the kidneys, bone marrow, and liver for male and female rats administered 250 mg/kg; the liver and kidneys of rats administered 125 mg/kg; the liver, kidneys, spleen, thymus, and bone marrow of mice administered 125 mg/kg; and the liver of mice administered 60 mg/kg. For lipid content analysis, sections of frozen liver were prepared and stained with Oil Red O.

TWO-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and groups of 50 female mice were administered chlorobenzene in corn oil by gavage, 5 days per week for 103 weeks, at doses of 0 (vehicle control), 60, or 120 mg/kg. Groups of 50 male mice received doses of 0, 30, or 60 mg/kg on the same schedule. Untreated controls consisted of 50 male and 50 female rats and mice.

Source and Specifications of Test Animals

Four-week-old F344/N rats and hybrid B6C3F$_1$ (C57BL/6N × C3H/HeN MTV−) mice were obtained from Charles River Breeding Laboratories, observed for approximately 2 weeks in quarantine, and assigned to cages according to a table of random numbers. The cages were also assigned to dosed and vehicle control groups according to a table of random numbers.

A quality control skin grafting program has been in effect since early 1968 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Bioassay Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic homogeneity via isozyme and protein electrophoregrams which demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of 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 those 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 non-uniformity in the hybrid mice on the test results is not known, but should not affect the validity of the studies since matched concurrent controls were included.

Sentinel Animals*

Rodents used in the Bioassay Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may have an impact on the testing data. The sentinel animal program is a key aspect of periodic disease monitoring of the animals. Under this program, the disease state of the rodents is monitored via viral serology from extra (sentinel) animals in the test rooms. These animals are untreated, but are exposed to the same environment as are the test animals. The sentinel animals originate from the same production source and weanling groups as the animals used for the bioassay.

Fifteen B6C3F$_1$ mice of both sexes and fifteen F344/N rats of both sexes were selected at the time of randomization and allocation of animals to the various study groups. These animals were designated as sentinel animals, housed in the same animal room as were the test animals, and subjected to the same experimental conditions (with the exception that neither the test material nor the vehicle was administered). These animals were sacrificed and bled according to the following schedule. Five animals of each group were killed at 6, 12, and 18 months of study. For the 24 month data points, 5/50 control animals of each sex and species were randomly selected for bleeding. The blood from each animal was collected, allowed to clot and the serum was separated. The serum was diluted 1:5 with buffered saline and shipped to the Murine Virus Diagnostic Laboratory of Microbiological Associates for determination of the viral titers.

* Since the precise significance of elevated viral antibody titers to rodent response to chemical toxicants is unknown at present, attempts to interpret the possible effect of elevated titers on the findings of this study will not be made. The data are listed in Appendix J, however, for future reference.

The following screens were performed:

	Hemagglutination Inhibition	Complement Fixation	Elisa*
Mice	PVM (Pneumonia virus of mice)	M. Ad. (Mouse adenovirus)	MHV (Mouse hepatitis virus)
	Reo 3 (Reovirus 3)	LCM (Lymphocytic choriomeningitis virus)	
	GDVII (Theiler's encephalomyelitis virus)		
	Poly (Polyoma virus)		
	Sendai (Sendai virus)		
	MVM (Minute virus of mice)		
	Ectro (Ectromelia virus)		
Rats	PVM (Pneumonia virus of mice)	RCV (Rat corona virus)	
	Sendai (Sendai virus)		
	KRV (Kilham rat virus)		
	H-1 (Toolan's H-1 virus)		

*Elisa = Enzyme-linked immunosorbent assay

The viral antibody titers in serum from sentinel animals in this study are summarized in Appendix J.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with polyester filter sheets (Table 2). Cages and bedding were replaced twice per week. Feed and water were available *ad libitum*.

The temperature in the animal room was 20°-26°C and the humidity was 40%-70%. Fifteen changes of room air per hour were provided. Fluorescent lighting was provided 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for mortality and moribundity. Clinical signs were recorded daily. Individual body weights were recorded once per week for the first 13 weeks and then monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the study were killed and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. 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 2.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. 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 in each group. The classification of proliferative lesions of the liver in rats was performed according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980).

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechniques were evaluated. All tumor diagnoses, target tissues for neoplastic change, and tissues from a randomly selected

10% of the animals were evaluated by an experienced rodent pathologist. Slides of all neoplastic target tissues and those on which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the PWG Chairperson were reviewed in a blind fashion by the PWG's pathologists, who reached a consensus and compared their findings with the original diagnoses. When conflicts arose, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described, in part, by Ward et al., 1978; and Maronpot and Boorman, 1982). The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Sections of livers from all male and female rats were reread in a blind fashion by an independent pathologist due to the equivocal nature of the nonneoplastic liver changes. The diagnoses of both pathologists (original and second) are illustrated.

Data Recording and Statistical Methods

All clinical chemistry, hematologic, and organ weight data were analyzed using Dunnett's multiple comparison test (Miller, 1981). Data on the 2-year 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, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. All animals dying from accidental causes were statistically censored at the time of death. 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) extensions of Cox's methods for testing for a dose-related trend. All reported P values for the survival analysis are two-sided.

The incidence of neoplastic or nonneoplastic lesions has been 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 that 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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high and low dose groups with controls and tests for overall dose-response trends.

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 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 methods 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 second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values for the tumor incidence analyses are one-sided.

For studies in which there is little effect of compound administration on survival, the results of the three alternate 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.

Statistical analyses employed only the vehicle controls, unless specified otherwise.

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	250, 500, 1,000, 2,000, or 4,000 mg/kg in corn oil by gavage; dose vol., 5 ml/kg	Rats: 0, 125, 250, 500, 1,000, or 2,000 mg/kg in corn oil by gavage; dose vol., 5 ml/kg Mice: 0, 30, 60, 125, 250, or 500 mg/kg in corn oil by gavage; dose vol., 5 ml/kg	0, 60, 125, 250, 500, or 750 mg/kg in corn oil by gavage; dose vol., 5 ml/kg	Rats: 0, 60, or 120 mg/kg in corn oil by gavage; dose vol., 5 ml/kg Mice: Females, 0, 60, or 120 mg/kg; dose vol., 5 ml/kg. Males: 0, 30, or 60 mg/kg; dose vol., 5 ml/kg
Duration of Dosing	Single dose	Fourteen consecutive days	Five days per week for 13 weeks	Five days per week for 103 weeks
Type and Frequency of Observation	Observed twice daily for clinical signs of toxicity	Observed twice daily for clinical signs of toxicity	Observed twice daily for mortality and morbidity; individual animal weights measured weekly	Observed twice daily for mortality and moribundity; weighed weekly for 13 weeks then monthly
Necropsy and Histologic Examination	No necropsies performed	Necropsies performed on all animals	Necropsies performed on all animals; control, 500, and 750 mg/kg rats and control, 250, 500, and 750 mg/kg mice examined histopathologically (selected tissues).	Necropsies and histopathological examinations performed on all animals, including: gross lesions, tissue masses, mandibular lymph nodes, salivary gland, sternebrae (including marrow), thyroid, parathyroid, small intestine, colon, liver, gallbladder (mice), seminal vesicles/prostate/testes or ovaries/uterus, lungs and mainstem bronchi, mammary gland, heart, esophagus, stomach, skin, brain, thymus, trachea, pancreas, spleen, kidneys, adrenals, urinary bladder, and pituitary.

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Animals and Animal Maintenance				
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
Animal Source	Harlan Industries (Indianapolis, IN)	Same as single-dose study	Same as single-dose study	Charles River Breeding Laboratories (Portage, MI)
Time Held Before Start of Test	16 days	Rats: 14 days Mice: 15 days	14 days	Rats: 17 days Mice: 14 days
Age When Placed on Study	Rats: 6 weeks Mice: 5-6 weeks	Rats: 6 weeks Mice: 7 weeks	Rats: 6 weeks Mice: 7 weeks	7 weeks
Age When Killed	Rats: 8 weeks Mice: 7-8 weeks	Rats: 8 weeks Mice: 9 weeks	Rats: 19 weeks Mice: 20 weeks	111 weeks
Method of Animal Distribution	Assigned by species and sex to cages according to table of random numbers; cages assigned to control and dosed groups according to another table of random numbers	Same as single-dose study	Same as single-dose study	Same as single-dose study
Feed	Purina® Laboratory Chow (pellets), Ralston Purina Co. (St. Louis, MO)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Bedding	Ab-sorb-dri® hardwood chips, Lab Products, Inc. (Garfield, NJ)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Water	Edstrom automatic watering system (Waterford, WI)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Cages	Polycarbonate Lab Products, Inc. (Garfield, NJ)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Cage Filters	Spun-bonded polyester (Dupont 2024)	Same as single-dose study	Same as single-dose study	Same as single-dose study

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Animals Per Cage	Five	Five	Five	Five
Animal Room Environment	21°-23°C; 40%-60% relative humidity; 12 hrs fluorescent light per day; 15 room air changes per hr	Same as single-dose study	Same as single-dose study	20° to 26°C; 40%-70% relative humidity; 15 room air changes per hr; 12 hrs fluorescent light per day
Other Chemicals on Test in Same Room	—	—	None	None
Chemical/Vehicle Mixture				
Preparation	Weighed quantity of chlorobenzene adjusted to highest dose level by mixing with corn oil in volumetric flask. Lower dose levels prepared by dilution of measured volume of high dose formulation with corn oil	Same as single-dose study	Chlorobenzene mixed with corn oil (w/v) to prepare highest dose; mixture stirred for 15 minutes. Lower dose levels prepared by sequential dilution of measured volume of high dose formulation with corn oil	Same as 13-week study
Maximum Storage Time	—	Prepared weekly	Prepared weekly	12 days
Storage Conditions	—	—	—	4°C until day of use

III. RESULTS

RATS

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Antibody Titers

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Antibody Titers

Survival

Pathology and Statistical Analyses of Results

SINGLE-DOSE STUDIES

Three of five males and 4/5 females administered 4,000 mg/kg chlorobenzene died on day 2 (Table 3). Another male rat in each of the 2,000 and 500 mg/kg groups died on day 2, as did two females in the 1000 mg/kg group on day 3. Hunched back, ataxia, labored breathing, and prostration were observed for 6 hours after the rats received the 4,000 mg/kg dose; these effects were present to a lesser extent in animals administered 2,000 mg/kg, but not in lower dose animals. Necropsies were not performed in this study.

FOURTEEN-DAY STUDIES

All rats receiving 1,000 or 2,000 mg/kg died by the end of the study, many during the first few days of treatment (Table 4). The rats receiving 2,000 mg/kg often became prostrate and failed to respond to external stimuli after chemical administration. These effects reversed partially within 6 hours and were absent within 24 hours post-dosing. Similar, but much milder, effects were observed in the rats at 1,000 mg/kg.

THIRTEEN-WEEK STUDIES

Nine of ten males and 8/10 females that received 750 mg/kg, and 4/10 males and 3/10 females that received 500 mg/kg died before the end of the study. Most of the deaths occurred during the latter half of the study (Table 5). Final mean body weights were depressed by 10% or more relative to controls for males that received 250 mg/kg or more, and for females that received 500 mg/kg or more.

Compound-related changes in hematological parameters were not observed, except for a decreased white blood cell count in the two surviving female rats at 750 mg/kg and an increased reticulocyte percentage in the surviving male rat at this dose (Appendix F, Table F1). Gamma-glutamyl transpeptidase (GGTP) and alkaline phosphatase activities were increased slightly in females receiving 500 or 750 mg/kg but no consistent effects were observed on the other serum chemistries (Appendix F, Table F2).

Due to early deaths, the numbers of individual urine samples obtained were 9, 7 and 4 for male rats in the control, 500 and 750 mg/kg groups, and 10, 7 and 2 for female rats in the control, 500 and 750 mg/kg groups. Twenty-four hour urine output was increased more than twofold in male rats at 750 mg/kg (Appendix F, Table F3).

Urinary uroporphyrin excretion was increased in male rats at 750 mg/kg, and urinary coproporphyrin excretion was increased in male rats at 500 and 750 mg/kg and in female rats at 500 mg/kg (Appendix F, Table F3). (The lack of a statistically significant increase in coproporphyrin excretion in female rats at 750 mg/kg may have been related to the small sample size). Changes were not observed in hepatic total porphyrin concentrations in the rats (Appendix F, Table F3).

At terminal sacrifice, liver- and kidney-to-body weight ratios were increased in male and female rats treated with the higher chlorobenzene doses (liver, 125 (females, only), 250, 500 and 750 mg/kg; kidney, 500 and 750 mg/kg) (Appendix F, Tables F4 and F5). In male rats, absolute liver and kidney weights were not increased, and the relative organ weights were increased only in those groups where body weight was depressed. In female rats, absolute kidney weight was increased only in the surviving animal at 750 mg/kg, but absolute liver weights were increased at all chlorobenzene doses except 60 mg/kg. Absolute and relative splenic weights were decreased in all chlorobenzene-treated groups of male rats (Appendix F, Table F4).

TABLE 3. SURVIVAL OF RATS ADMINISTERED A SINGLE DOSE OF CHLOROBENZENE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Survival (Day of Death)	
	Males	Females
250	5/5	5/5
500	4/5 (2)	5/5
1,000	5/5	3/5 (3,3)
2,000	4/5 (2)	5/5
4,000	2/5 (2,2,2)	1/5 (2,2,2,2)

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED CHLOROBENZENE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)* (day of death)	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
MALES					
0	5/5	126	138	+12	—
125	5/5	117	149	+32	+ 8
250	5/5	111	144	+33	+ 4
500	5/5	115	143	+28	+ 4
1,000	0/5 (3,4,10,14,15)	108	—	—	—
2,000	0/5 (3,3,3,3,4)	109	—	—	—
FEMALES					
0	5/5	106	124	+18	—
125	5/5	103	122	+19	- 2
250	5/5	99	118	+19	- 5
500	5/5	96	110	+14	-11
1,000	0/5 (4,6,10,11,14)	98	—	—	—
2,000	0/5 (1,2,4,4,6)	95	—	—	—

(a) Number surviving/number per group.

(b) Weight of the Dosed Group Relative to Controls ◘

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED CHLOROBENZENE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
MALES					
0	9/10 *(d)*	116 ± 4	294 ± 2	178 ± 4	—
60	10/10	117 ± 3	286 ± 7	169 ± 7	- 3
125	10/10	118 ± 2	281 ± 5	163 ± 4	- 4
250	10/10	118 ± 3	258 ± 5	140 ± 5	-12
500	6/10 *(d)*	126 ± 2	257 ± 13	132 ± 12	-13
750	1/10 *(d)*	120	257	137	-13
FEMALES					
0	10/10	105 ± 2	174 ± 4	69 ± 3	—
60	10/10	101 ± 1	175 ± 4	74 ± 4	+ 1
125	10/10	101 ± 1	178 ± 4	77 ± 4	+ 2
250	10/10	103 ± 2	178 ± 3	75 ± 3	+ 2
500	7/10 *(e)*	100 ± 2	153 ± 8	53 ± 8	-12
750	2/10 *(e)*	110 ± 8	140 ± 20	30 ± 28	-19

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight of the Dosed Group Relative to the Controls =

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) The weeks of the study during which the individual male rats died were: 750 mg/kg - 1, 4, 8, 10, 11, 11, 13, 13, 13; 500 mg kg - 4, 8, 11, 13; 0 mg/kg - 4.

(e) The weeks of the study during which the individual female rats died were: 750 mg/kg - 8, 8, 8, 8, 8, 8, 10, 12; 500 mg/kg - 6, 10, 11.

Histologic examinations revealed chemically related changes in the liver, kidney, bone marrow, spleen, and thymus. These changes were most apparent in the 500 and 750 mg/kg groups (Table 6). Histopathologic lesions were graded according to perceived severity on a scale of minimal, mild, moderate, and severe. The liver lesions consisted primarily of centrilobular hepatocellular necrosis. (Increased staining with Oil Red O indicated that the lipid content of the liver was increased in this area.) The severities of the liver lesions were diagnosed as moderate at 750 mg/kg, minimal to moderate at 500 mg/kg, and minimal at 250 mg/kg, for both sexes of rats.

Nephropathy was observed in both male and female rats at 750 mg/kg and in male rats at 500 mg/kg. The lesion was judged to be mild to moderate in severity. This "nephrosis" was characterized by proximal tubular degeneration and necrosis. The degeneration consisted of vacuolated tubular epithelial cells with indistinct cellular borders. Fragments of these epithelial cells often appeared to protrude into the lumen of the tubule. The distribution of degenerated cells within the kidney was diffuse. A number of granular and proteinaceous casts were present in distal tubules. Coagulative necrosis of tubular epithelial cells occurred in foci, generally involving 6-12 adjacent tubules. The severity of the necrosis varied considerably from animal to animal. Tubular regeneration was observed in two female rats at 750 mg/kg.

TABLE 6. INCIDENCE OF HISTOPATHOLOGIC LESIONS IN RATS ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose (mg/kg)	Sex	Lesion					
		Hepatic Necrosis	Hepatic Degeneration	Bone Marrow-Myeloid Depletion	Spleen-Lymphoid Depletion	Thymus-Lymphoid Depletion	Nephropathy
VEHICLE CONTROL	M	0/10	0/10	0/10	0/10	0/10	0/10
	F	0/10	0/10	0/10	0/10	0/10	0/10
125	M	0/10	0/10	*(a)*	*(a)*	*(a)*	0/10
	F	0/10	0/10	*(a)*	*(a)*	*(a)*	0/10
250	M	2/10	0/10	0/10	0/10	0/10	1/10
	F	1/10	0/10	0/10	0/10	0/10	0/10
500	M	3/10	2/10	3/10	0/10	0/10	2/10
	F	1/10	0/10	2/10	0/10	1/10	0/10
750	M	7/10	1/10	7/10	4/10	2/10	2/10
	F	6/10	4/10	9/10	4/10	1/10	7/10

(a) Tissue not examined due to the lack of effect at the next higher dose.

Lymphoid depletions of the thymus (mild to moderate) and spleen (minimal to mild) were observed in both sexes of rats at 750 mg/kg, and myeloid depletion of the bone marrow (minimal to moderate) was observed in both sexes at 500 and 750 mg/kg.

Doses of 60 and 120 mg/kg chlorobenzene were selected for rats in the 2-year studies based on the following results from the short-term testing:

1. Decreased survival at 500 and 750 mg/kg/day.
2. Marginal to moderate depressions in body weight gains at 500 and 750 mg/kg/day.
3. Dose-dependent hepatocellular necrosis at 250, 500 and 750 mg/kg/day.
4. Nephrotoxicity, and lymphoid or myeloid depletion of the spleen, bone marrow, and thymus at 500 and 750 mg/kg/day.
5. Scattered changes in urinary and clinical chemistry, hematology, organ weight, and porphyrin metabolism parameters at 500 and 750 mg/kg/day.

TWO-YEAR STUDIES

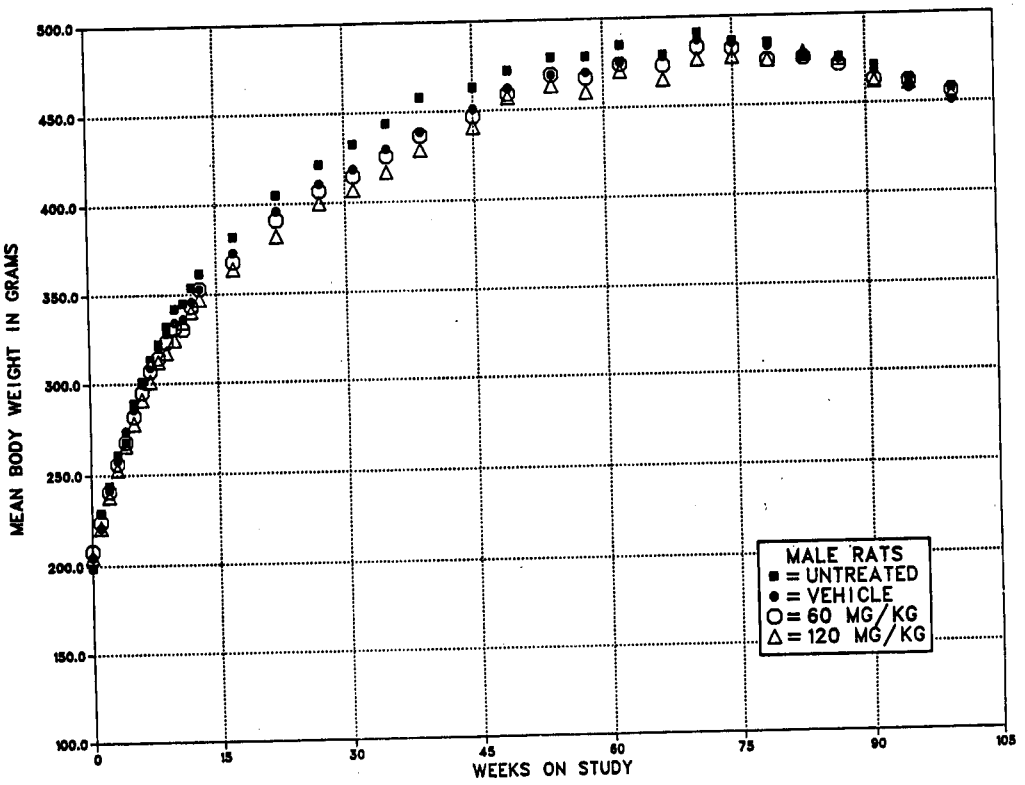
Body Weights and Clinical Signs

Throughout the studies, mean body weights of dosed and vehicle control male rats were comparable (Figure 2, and Appendix G, Table G1). During the second year of the studies, mean body weights of dosed female rats were greater than those of the vehicle controls. No compound-related clinical signs of toxicity were observed at any time during the studies.

Antibody Titers

Viral antibody titers are shown in Appendix J. Positive titers of KRV (Kilham Rat Virus) were detected at 24 months*.

* The significance of elevated viral antibody titers to the evaluation of animal response to chemical exposure is unknown at this time.



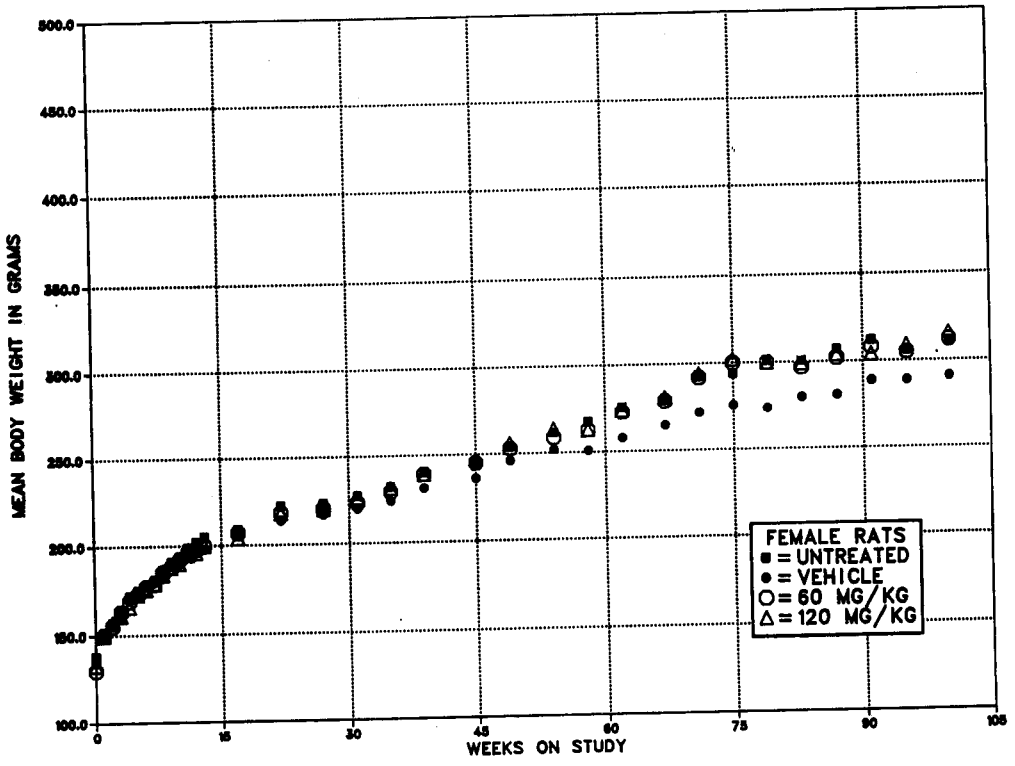


Figure 2. Growth Curves for Rats Administered Chlorobenzene by Gavage

Survival

Estimates of the probabilities of survival of male and female rats administered chlorobenzene in corn oil at the doses of this bioassay, and those of the vehicle controls, are shown in Figure 3. The survival of high dose male rats was significantly less than that observed for the vehicle controls (P=0.033). No other significant differences in survival were observed.

In male rats, 48/50 (96%) of the untreated controls, 49/50 (98%) of the vehicle controls, 45/50 (90%) of the low dose, and 41/50 (82%) of the high dose animals were alive at 78 weeks. In female rats, 48/50 (96%) of the untreated controls, 39/50 (78%) of the vehicle controls, 37/50 (74%) of the low dose, and 40/50 (80%) of the high dose animals were alive at 78 weeks.

In male rats, 34/50 (68%) of the untreated controls, 39/50 (78%) of the vehicle controls, 32/50 (64%) of the low dose, and 26/50 (52%) of the high dose group lived to the end of the study at 104 weeks. In female rats, 37/50 (74%) of the untreated controls, 29/50 (58%) of the vehicle controls, 30/50 (60%) of the low dose, and 31/50 (62%) of the high dose group lived to the end of the study.

There were 0, 2, 6 and 9 accidental deaths diagnosed in male rats in the untreated, vehicle control, low dose and high dose groups, respectively, and 0, 8, 9 and 7 accidental deaths diagnosed in female rats in the untreated, vehicle control, low dose and high dose groups, respectively. All of these deaths were considered to be related to gavage technique. One of the 17 accidental deaths in male rats and 11 of the 24 accidental deaths in female rats occurred during week 29 of the study. They were all attributed to replacement of the 3-inch feeding needles normally used for gavage administration with 4-inch needles. Return to the use of 3-inch needles greatly reduced the frequency of accidental deaths.

One low dose male rat, one high dose male rat, one low dose female rat, and two high dose female rats were suspected of dying from gavage-related trauma, although the observations were not definitive. Also the carcasses of two high dose male rats that died early were too autolyzed to determine a likely cause of death. For statistical purposes, all of these animals were considered non-accidental deaths.

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Appendix A, Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Historical incidences of tumors in control animals are listed in Appendix H. Appendix I, Tables I1 and I2, contain 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 are discussed in chapter II (Data Recording and Statistical Methods) and Appendix I (footnotes).

Liver: An apparent increase in the occurrence of hepatocellular necrosis, and decreases in the occurrences of hepatocellular basophilic cytoplasmic change and granulomatous inflammation, were observed in chlorobenzene-treated male and female rats (Table 7). Upon a blind review of all liver sections by an independent pathologist, however, the occurrence of hepatocellular necrosis in chlorobenzene-treated rats was found to be similar to that in controls (Table 7). Both diagnosticians generally graded the necrotic lesions as minimal to mild in severity in all groups. Therefore, the evidence for mild chlorobenzene-induced hepatocellular necrosis in these studies is considered equivocal.

According to the review of the liver sections, the number of sections with multiple basophilic foci (basophilic cytoplasmic change) was greater in the untreated and vehicle controls than in the chlorobenzene-treated male and female rats, and the number of foci per section in those sections with multiple foci was also greater in the control than in the treated groups (data not shown).

Neoplastic nodules occurred in male rats with a significant positive trend, and the incidence of animals with neoplastic nodules was significantly higher in the high dose group than in the vehicle controls by all tests (Table 8). Hepatocellular carcinomas were not observed in chlorobenzene-dosed male rats; the combined incidence of neoplastic nodules or carcinomas was increased by life table analyses (trend test, and pairwise comparison of vehicle control and high dose groups). Increases in neoplastic nodules, hepatocellular carcinomas, or combined neoplastic nodules or hepatocellular carcinomas were not observed in female rats.

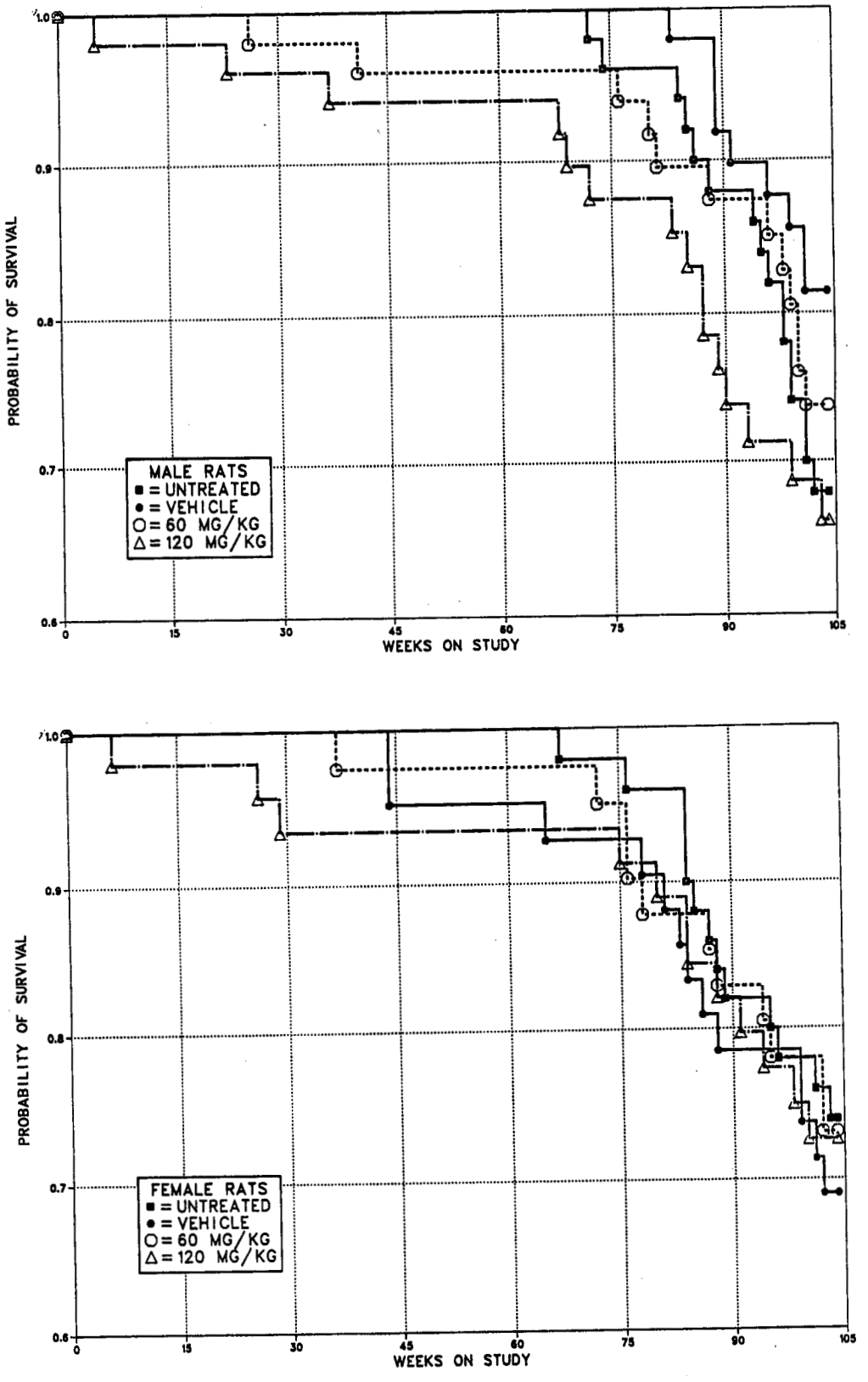


Figure 3. Kaplan-Meier Survival Curves for Rats Administered Chlorobenzene by Gavage

TABLE 7. NUMBERS OF RATS WITH NONNEOPLASTIC LIVER LESIONS

	MALES				FEMALES			
Livers Examined:	Untreated Control 50	Vehicle Control 50	60 mg/kg 49	120 mg/kg 49	Untreated Control 49	Vehicle Control 50	60 mg/kg 50	120 mg/kg 50
First Diagnosis (Original)								
Lesions								
Hepatocellular Necrosis *(a)*	2	1	4	5	0	0	1	7
Cytoplasmic (Basophilic) Change	25	27	6	3	38	27	18	10
Inflammation (Focal, Granulomatous)	9	9	3	0	23	21	11	11
Second Diagnosis (Independent Review)								
Hepatocellular Necrosis *(a)*	3	2	5	1	1	1	2	1
Cytoplasmic (Basophilic) Change	28	40	12	12	43	34	26	18

(a) Considered to be minimal to mild in severity.

TABLE 8. ANALYSIS OF LIVER TUMORS IN MALE RATS: STATISTICAL COMPARISONS OF TREATED TO VEHICLE CONTROLS

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Neoplastic Nodule				
Tumor Rates				
Overall	4/50 (8%)	2/50 (4%)	4/49 (8%)	8/49 (16%)
Adjusted	10.4%	4.5%	12.5%	29.3%
Terminal	2/34 (6%)	0/39 (0%)	4/32 (13%)	7/26 (27%)
Statistical Tests				
Life Table		P=0.005	P=0.255	P=0.010
Incidental Tumor Test		P=0.011	P=0.290	P=0.021
Cochran-Armitage Trend Test		P=0.027		
Fisher Exact Test			P=0.329	P=0.043
Carcinoma				
Tumor Rates				
Overall	0/50 (0%)	2/50 (4%)	0/49 (0%)	0/49 (0%)
Adjusted	0.0%	5.1%	0.0%	0.0%
Terminal	0/34 (0%)	2/39 (5%)	0/32 (0%)	0/26 (0%)
Statistical Tests				
Life Table		P=0.139N	P=0.283N	P=0.331N
Incidental Tumor Test		P=0.139N	P=0.283N	P=0.331N
Cochran-Armitage Trend Test		P=0.098N		
Fisher Exact Test			P=0.253N	P=0.253N
Neoplastic Nodule or Carcinoma				
Tumor Rates				
Overall	4/50 (8%)	4/50 (8%)	4/49 (8%)	8/49 (16%)
Adjusted	10.4%	9.4%	12.5%	29.3%
Terminal	2/34 (6%)	2/39 (5%)	4/32 (13%)	7/26 (27%)
Statistical Tests				
Life Table		P=0.033	P=0.532	P=0.048
Incidental Tumor Test		P=0.054	P=0.570	P=0.083
Cochran-Armitage Trend Test		P=0.121		
Fisher Exact Test			P=0.631	P=0.168

Lung: The aspiration of foreign bodies into the lung in both sexes of rats, and acute/chronic inflammation of the lung in female rats, were diagnosed at increased occurrences in the chlorobenzene-treated animals (Table 9). One of the 2 vehicle control male rats, 5 of the 15 low dose male rats, 7 of the 10 high dose male rats, 4 of the 5 low dose female rats, and 5 of the 9 high dose female rats with foreign materials in the lung were considered to have died from gavage-related trauma. In contrast, the diagnosed occurrences of focal granulomatous inflammation of the lung were reduced by chlorobenzene administration in both sexes of rats (Table 9). Diagnoses of foreign body aspiration and focal granulomatous inflammation were not made for untreated control rats (Table 9).

Testis: Interstitial cell tumors were observed with a significant positive trend by the life table test, and the incidence in the high dose group was significantly higher than that in the vehicle controls by the life table test (Appendix I, Table I1). Statistical significance was not indicated by either the incidental tumor or Fisher exact tests. One of the interstitial cell tumors in a vehicle control rat was malignant; none of the tumors in the dosed groups were malignant.

Urinary Bladder: A transitional cell papilloma was found in 1/46 (2%) low dose and 1/45 (2%) high dose male rats. This tumor type was not observed in untreated or vehicle controls.

Kidney: A tubular cell adenocarcinoma was observed in one high dose female rat. This tumor type was not observed in untreated controls, vehicle controls, or low dose female rats.

Pituitary: Adenomas in female rats, and adenomas, adenocarcinomas, or carcinomas (combined) in male rats occurred with significant negative trends (Table 10). The incidences in the high dose groups were significantly lower than those in the controls.

Uterus: Endometrial stromal polyps were observed with a significantly lower incidence in the low dose group than in the controls (Table I1).

TABLE 9. COMPARATIVE INCIDENCES OF LUNG LESIONS IN MALE AND FEMALE RATS

Group:	MALES *(a)*				FEMALES *(a)*			
	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
No. of lungs Examined	50	50	50	50	47	49	49	49
LESION								
Aspiration, foreign body	0 (0) *(b)*	4 (3)	15 (10)	10 (3)	0 (0)	0 (0)	5 (1)	9 (4)
Inflammation, acute/chronic	7	2	9	4	2	1	7	11
Inflammation, focal granulomatous	0	11	4	1	0	14	8	2

(a) Number of animals with the specified lesion.
(b) The numbers in parentheses include only those animals that were not diagnosed as having died from gavage accidents.

TABLE 10. ANALYSIS OF PITUITARY TUMORS IN RATS

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
MALES				
Adenoma				
Tumor Rates				
Overall	20/49 (41%)	10/50 (20%)	9/42 (21%)	3/47 (6%)
Adjusted	47.5%	24.2%	27.4%	10.6%
Terminal	12/33 (36%)	8/39 (21%)	7/30 (23%)	2/25 (8%)
Statistical Tests				
Life Table		P=0.172N	P=0.477	P=0.162N
Incidental Tumor Test		P=0.109N	P=0.532	P=0.101N
Cochran-Armitage Trend Test		P=0.047N		
Fisher Exact Test			P=0.534	P=0.046N
Adenoma, Adenocarcinoma or Carcinoma				
Tumor Rates				
Overall	20/49 (41%)	12/50 (24%)	9/42 (21%)	3/47 (6%)
Adjusted	47.5%	28.3%	27.4%	10.6%
Terminal	12/33 (36%)	9/39 (23%)	7/30 (23%)	2/25 (8%)
Statistical Tests				
Life Table		P=0.084N	P=0.541N	P=0.086N
Incidental Tumor Test		P=0.044N	P=0.462N	P=0.044N
Cochran-Armitage Trend Test		P=0.016N		
Fisher Exact Test			P=0.484N	P=0.015N
FEMALES				
Adenoma				
Tumor Rates				
Overall	27/48 (56%)	23/46 (50%)	18/46 (39%)	13/43 (30%)
Adjusted	63.6%	67.0%	56.1%	41.6%
Terminal	20/35 (57%)	16/27 (59%)	15/29 (52%)	9/26 (35%)
Statistical Tests				
Life Table		P=0.027N	P=0.146N	P=0.039N
Incidental Tumor Test		P=0.016N	P=0.252N	P=0.021N
Cochran-Armitage Trend Test		P=0.036N		
Fisher Exact Test			P=0.201N	P=0.046N

TABLE 11. ANALYSIS OF ENDOMETRIAL STROMAL POLYPS OF THE UTERUS IN FEMALE RATS

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Tumor Rates				
Overall	9/49 (18%)	16/50 (32%)	4/49 (8%)	10/50 (20%)
Adjusted	23.2%	51.3%	13.3%	29.3%
Terminal	7/36 (19%)	14/29 (48%)	4/30 (13%)	8/31 (26%)
Statistical Tests				
Life Table		P=0.060N	P=0.002N	P=0.090N
Incidental Tumor Test		P=0.059N	P=0.002N	P=0.088N
Cochran-Armitage Trend Test		P=0.085N		
Fisher Exact Test			P=0.003N	P=0.127N

SINGLE-DOSE STUDIES

All male and female mice administered 2,000 or 4,000 mg/kg and all male mice administered 1,000 mg/kg died within 3 days (Table 12). At least one death occurred in all dosed groups except for female mice receiving 500 mg/kg. Hyperpnea was observed in nearly all of the dosed mice shortly after treatment. This effect had reversed within 24 hours. Necropsies or histological analyses were not performed. The cause of death in these studies are unknown.

FOURTEEN-DAY STUDIES

Although several deaths occurred during the repeated-dose studies (Table 13), none were considered to be clearly compound related due to the lack of chemical-related gross pathologic effects. Clinical signs of toxicity were not observed at any time during the studies. Chemical-related effects were not observed at necropsy of the study survivors. Histological analyses of the tissues were not performed.

THIRTEEN-WEEK STUDIES

All males that received 500 or 750 mg/kg died during the first week of the study, while all females that received 750 mg/kg were dead by week 9 (Table 14). These data suggest that male mice might be more susceptible to the lethal effects of chlorobenzene than are female mice. Deaths also occurred in males at 250 mg/kg, and in females at 250 and 500 mg/kg. Final body weights appeared to be lowered in male mice at 250 mg/kg and in female mice at 500 mg/kg (Table 14).

The results of hematologic and clinical chemistry analyses failed to indicate any clear compound-related effects of chlorobenzene on the surviving mice (Appendix F, Tables F6 and F7). Due to early deaths and group caging, the numbers of individual urine samples obtained were 2, 2, and 1 for male mice in the control, 125, and 250 mg/kg groups, and 2, 1, and 2 for female mice in the control, 250, and 500 mg/kg groups. Group caging precluded reasonable statistical analysis of individual urine outputs. Consistent with the polyuria observed in male rats at 750 mg/kg, however, mean 24-hour urine volume per animal was 5 ml in 500 mg/kg female mice, compared to 2 ml in control female mice (data not shown). Urinary coproporphyrin excretion was increased at 250 and 500 mg/kg in female mice (Appendix F, Table F8). No changes were observed in liver total porphyrin concentrations in male or female mice.

At terminal sacrifice, the absolute and relative (to body weight) weights of the liver were increased in (surviving) male mice at 125 and 250 mg/kg, and in (surviving) female mice at 250 and 500 mg/kg (Appendix F, Tables F9 and F10). Absolute and relative heart weights were decreased slightly (less than 20%) in all chlorobenzene-treated groups of male mice.

TABLE 12. SURVIVAL OF MICE ADMINISTERED A SINGLE DOSE OF CHLOROBENZENE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Survival (Day of Death)	
	Male	Female
250	2/5 (3,3,4)	3/5 (4,10)
500	4/5 (2)	5/5
1,000	0/5 (2,2,2,2,3)	3/5 (3,3)
2,000	0/5 (1, *a*)(2,2,2,2)	0/5 (2,2,2,4,6)
4,000	0/5 (2,2,2,2,2)	0/5 (1, *a*)(2,2,2,2)

(a) Death was due to gavage-related trauma.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED CHLOROBENZENE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
MALES					
0	3/5 (6,7)	21	25	+4	—
30	5/5	22	24	+2	- 4
60	5/5	21	23	+2	- 8
125	4/5 (4) *(d)*	23	26	+3	+ 4
250	5/5	22	25	+3	0
500	3/5 (3,4) *(c)*	21	23	+2	- 8
FEMALES					
0	5/5	18	20	+2	—
30	5/5	18	20	+2	0
60	5/5	19	21	+2	+ 5
125	4/5 (3) *(d)*	18	21	+3	+ 5
250	5/5	19	23	+4	+15
500	5/5	18	20	+2	0

(a) Number surviving/number per group.

(b) Weight of the Dosed Group Relative to Controls =

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(c) Deaths not considered to be compound related.

(d) Gavage-related trauma.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED CHLOROBENZENE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weight (grams)			Final Body Weight Relative to Controls *(c)* (Percent)
		Initial	Final	Change *(b)*	
MALES					
0	10/10	24 ± 1	35 ± 1	11 ± 1	
60	10/10	24 ± 1	32 ± 0	8 ± 1	9
125	10/10	25 ± 1	33 ± 0	8 ± 1	- 6
250	4/ 9 *(e)*	26 ± 1 *(d)*	28 ± 2	2 ± 1	-20
500	0/10 *(e)*	—	—	—	—
750	0/10 *(e)*	—	—	—	—
FEMALES					
0	9/10 *(f)*	20 ± 1	26 ± 1	6 ± 1	—
60	10/10	21 ± 1	27 ± 0	6 ± 1	+ 4
125	10/10	20 ± 1	26 ± 1	7 ± 1	0
250	6/10 *(f)*	21 ± 1	24 ± 1	3 ± 1	- 8
500	3/10 *(f)*	19 ± 1	22 ± 1	3 ± 1	-15
750	0/10 *(f)*	—	—	—	—

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.

(b) Mean weight change of the survivors of the group ± standard error of the mean.

(c) Weight of the Dosed Group Relative to Controls =

$$\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$$

(d) The initial body weight was not recorded for one of the animals in this group.

(e) The weeks of the study during which the individual male mice died were: 750 mg/kg - all in week 1; 500 mg/kg - all in week 1; 250 mg/kg - 1, 10, 10, 10, 10.

(f) The weeks of the study during which the individual female mice died were: 750 mg/kg - 4, 6, 7, 8, 9, 9, 9, 9, 9, 9; 500 mg/kg - 11, 12, 12, 13, 13, 13, 13; 250 mg/kg - 11, 11, 11, 11; 0 mg/kg - 13.

Histologic examinations revealed dose-dependent chemical-induced injuries to the liver, kidney, bone marrow, spleen, and thymus (Table 15). The lesions were graded according to perceived severity on a scale of minimal, mild, moderate, and severe. Except for hepatic necrosis, which was also found in one male receiving 60 mg/kg and one male receiving 125 mg/kg, the lesions were observed only at the 250, 500, and 750 mg/kg doses (doses that also caused some deaths) in both sexes. Centrilobular hepatocellular necrosis occurred at the 500 and 750 mg/kg doses, and focal hepatocytic necrosis and degenerative changes in the centrilobular hepatocytes were observed at 250 mg/kg. All of the lesions were graded as severe at the 250, 500 and 750 mg/kg doses. (Increased staining with Oil Red O indicated that the lipid content of the liver was increased at these doses as well.)

Nephropathy was observed in male mice at 250, 500 and 750 mg/kg, and in female mice at 250 mg/kg. In male mice, the renal lesion consisted of mild to moderate necrosis of the proximal tubular epithelium at 500 and 750 mg/kg, and mild to moderate regeneration of the proximal tubules at 250 mg/kg. Tubular regeneration was also observed in female mice at 250 mg/kg, but tubular necrosis or other renal lesions were not observed in this sex even at higher chlorobenzene doses.

TABLE 15. INCIDENCE OF HISTOPATHOLOGIC LESIONS IN MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose (mg/kg)	Sex	Hepatic Necrosis	Hepatic Degeneration	Nephropathy	Bone Marrow-Myeloid Depletion	Spleen-Lymphoid Depletion	Spleen-Myeloid Depletion	Thymus-Lymphoid Necrosis	Thymus-Lymphoid Depletion
VEHICLE CONTROL	M	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	F	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
60	M	1/10	0/10	*(a)*	*(a)*	*(a)*	*(a)*	*(a)*	*(a)*
	F	0/10	0/10	*(a)*	*(a)*	*(a)*	*(a)*	*(a)*	*(a)*
125	M	1/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	F	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
250	M	7/10	2/10	4/10	4/10	4/10	4/10	4/10	0/10
	F	10/10	0/10	4/10	2/10	2/10	4/10	3/10	0/10
500	M	10/10	0/10	9/10	0/10	2/10	0/10	8/10	2/10
	F	8/10	9/10	0/10	3/10	3/10	4/10	0/10	3/10
750	M	10/10	0/10	8/10	0/10	5/10	0/10	5/10	4/10
	F	1/10	4/10	0/10	0/10	9/10	0/10	1/10	3/10

(a) Tissue not examined due to the absence of lesions at the next higher dose.

Myeloid depletion of the bone marrow occurred in mice of both sexes at doses of 250 mg/kg and higher. The lesions were considered to be minimal to mild in severity. Lymphoid depletion or necrosis of the thymus occurred in surviving mice of both sexes at doses of 250 mg/kg (necrosis) or 500 mg/kg (depletion) and greater; the severities of these changes were considered to be moderate to severe.

Doses of 60 and 120 mg/kg chlorobenzene were selected for female mice in the 2-year study based on the following results from the short-term study (doses of 30 and 60 mg/kg were selected for male mice because of a perceived greater susceptibility of this sex to the toxic effects of chlorobenzene):

1. Decreased survivals at 250, 500 and 750 mg/kg/day.
2. Dose-dependent hepatocellular necrosis at 250, 500 and 750 mg/kg/day.
3. Nephrotoxicity, thymic necrosis, and lymphoid or myeloid depletion of the thymus, spleen and bone marrow at doses of 250, 500 or 750 mg/kg/day.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control mice were comparable throughout the study (Figure 4 and Appendix G, Table G2). No compound-related clinical signs of toxicity were observed in this study.

Antibody Titers

Viral antibody titers are shown in Appendix J. Positive titers were observed at the following times: PVM (Pneumonia Virus of Mice), 18 months; GDVII (Theiler's Encephalomyelitis Virus), 24 months; MVM (Minute Virus of Mice), 18 months; Sendai Virus, 12 months; MHV (Mouse Hepatitis Virus), 6 and 24 months.*

Survival

Estimates of the probability of survival of male and female mice administered chlorobenzene in corn oil at the doses of these studies, and those of the vehicle controls, are shown in Figure 5. The survivals of the low and high dose groups of male mice were marginally less than those of the controls (P=0.044 and P=0.042 for low and high dose male mice, respectively). No other significant differences in survival were observed.

In male mice, 46/50 (92%) of the untreated controls, 48/50 (96%) of the vehicle controls, 42/50 (84%) of the low dose, and 43/50 (86%) of the high dose animals were alive at 78 weeks. In female mice, 49/50 (98%) of the untreated controls, 49/50 (98%) of the vehicle controls, 47/50 (94%) of the low dose, and 47/50 (94%) of the high dose animals were alive at 78 weeks.

In male mice, 35/50 (70%) of the untreated controls, 39/50 (78%) of the vehicle controls, 28/50 (56%) of the low dose, and 29/50 (58%) of the high dose group lived to the termination of the study at 105 weeks. In female mice, 37/50 (74%) of the untreated controls, 40/50 (80%) of the vehicle controls, 41/50 (82%) of the low dose, and 38/50 (76%) of the high dose group lived to the termination of the study at 105 weeks. The survival incidences include one high dose female that died during the termination of the study. For statistical purposes, this animal has been pooled with those killed at the end of the study.

Two low dose male mice, one high dose male mouse, and one high dose female mouse were diagnosed as having died from gavage-related traumas. The carcasses of one low dose male mouse and one high dose male mouse were too autolyzed for reasonable analysis of cause of death. For statistical purposes, these two mice were considered to have died from non-accidental causes.

* At the present time, the significance of elevated viral antibody titers to the evaluation of animal response to chemical exposure is unknown.

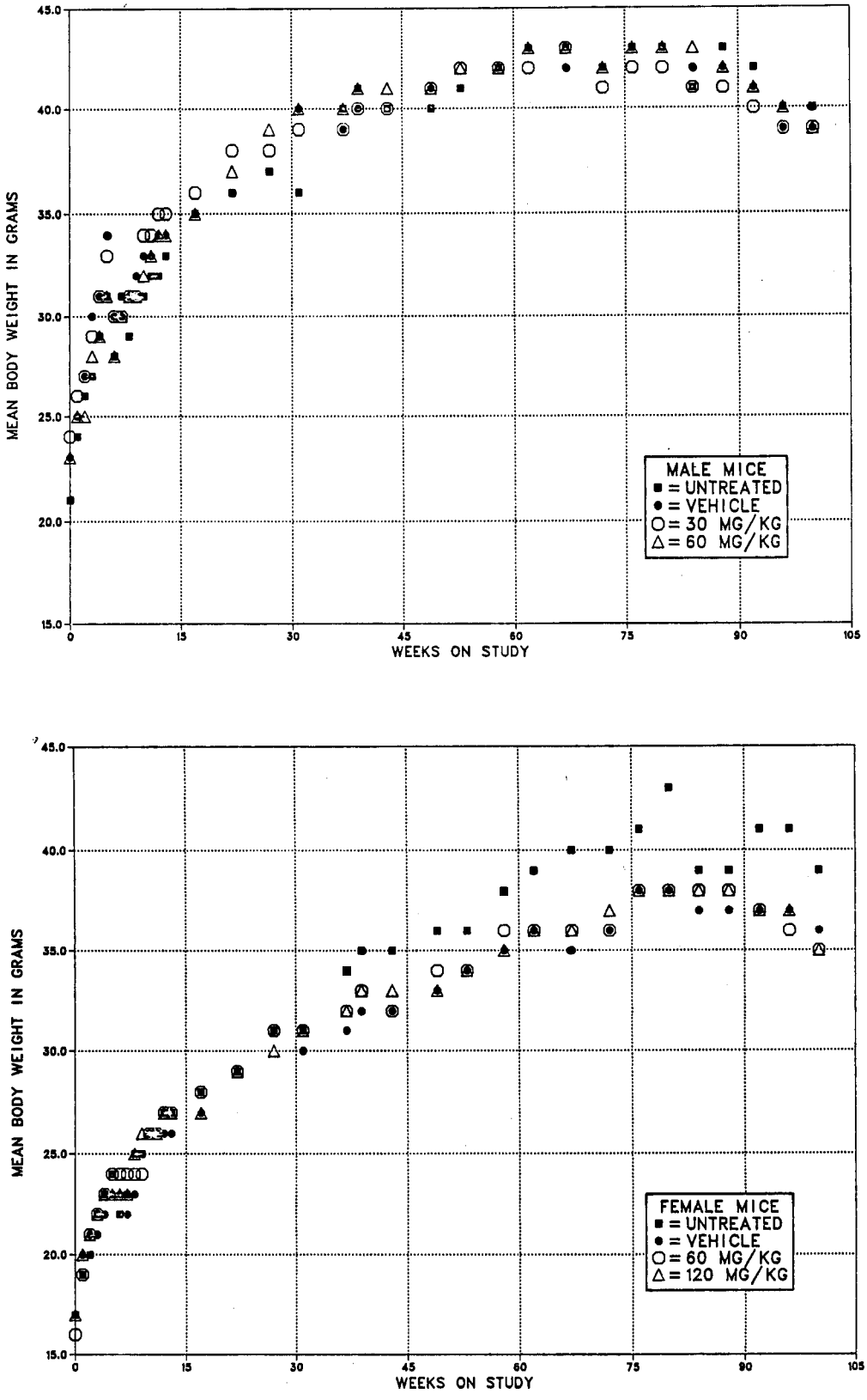


Figure 4. Growth Curves for Mice Administered Chlorobenzene by Gavage

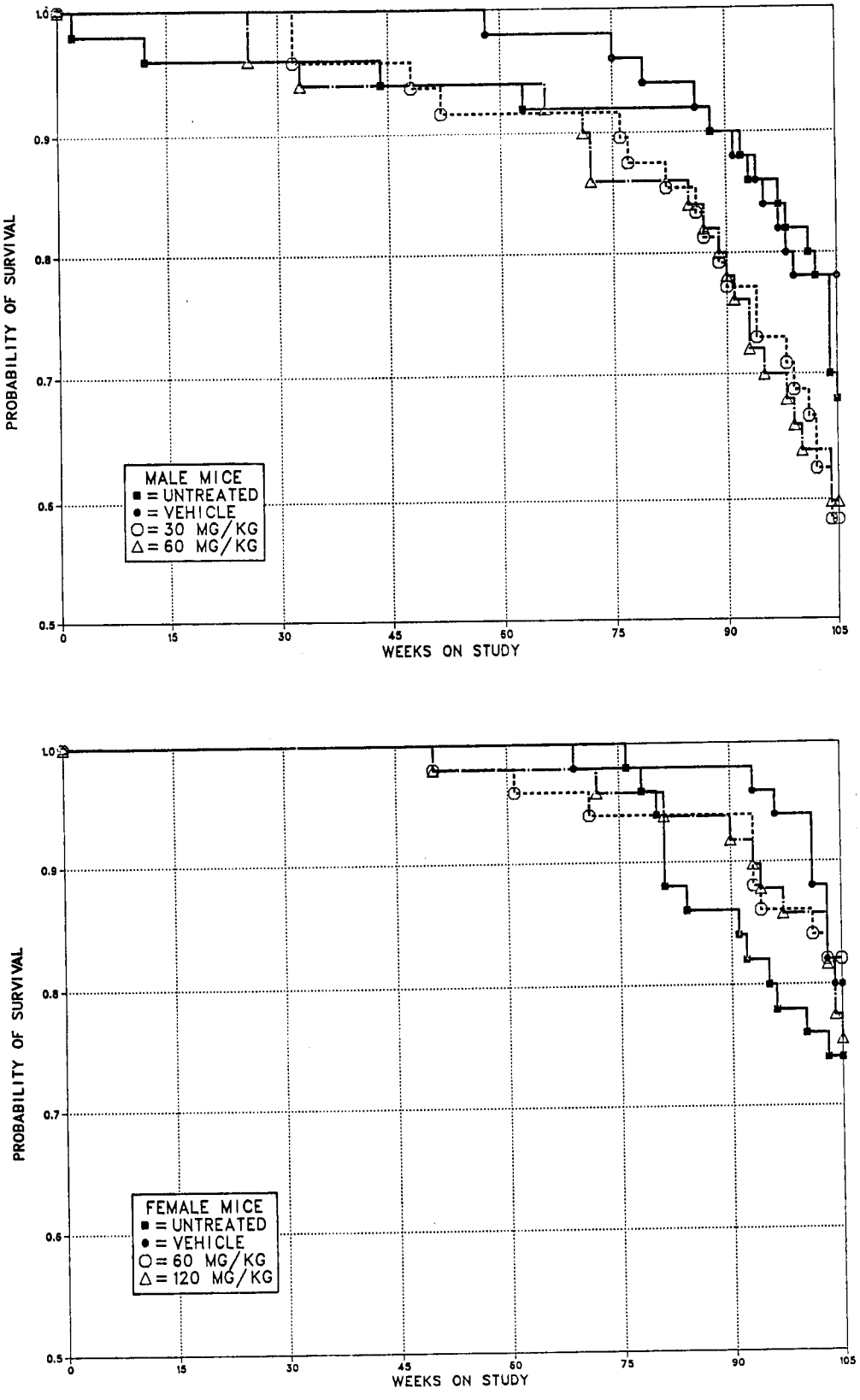


Figure 5. Kaplan-Meier Survival Curves for Mice Administered Chlorobenzene by Gavage

Pathology and Statistical Analyses of Results

Histopathologic findings of neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Appendix B, Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix I, Tables I3 and I4, contain 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 (Data Recording and Statistical Methods) and Appendix I (footnotes).

No site-specific tumors or nonneoplastic pathology occurred at statistically significant increased or decreased incidences in either male or female mice treated with chlorobenzene.

IV. DISCUSSION AND CONCLUSIONS

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Chlorobenzene was tested for toxic potential in male and female B6C3F$_1$ mice and Fischer 344 rats by oral administration in corn oil. The doses were 0 (vehicle control), 60, 125, 250, 500 or 750 mg/kg/day, 5 days per week (gavage), for both sexes and species in the 13-week studies. In the 2-year studies, doses of 0 (vehicle control), 60 or 120 mg/kg/day were administered to male and female rats and female mice, and doses of 0, 30 and 60 mg/kg/day to male mice, 5 days per week (gavage) for 103 weeks.

The results of the 13-week studies reported herein largely corroborate the earlier reports that chlorobenzene exposure can adversely affect the liver, kidneys, and hematopoietic system (see Introduction). Consistent changes in hematological parameters were not observed in this study despite microscopic evidence of myeloid and/or lymphoid depletion of the bone marrow in both rats and mice. Hematologic analyses were performed only on survivors at the end of the study, however, while the frequencies of the bone marrow lesions were generally greater in the early death animals than in those that survived until the end of the study (data not shown). Analyses at an earlier time, therefore, may have revealed chemical effects on circulating blood components not apparent in survivors after 90 days of treatment.

The increased liver total porphyrin concentrations at the higher chlorobenzene doses in female rats, and the general porphyrinuria in chlorobenzene-treated rats and mice in the 13-week studies suggest an effect on liver heme metabolism, as was indicated by the previous studies demonstrating increased hepatic ALA-synthetase activity in chlorobenzene-treated rats (see Introduction). Whatever the mechanism of the chlorobenzene effect on heme synthesis, the magnitude of the change was apparently insufficient to produce anemia or other severe hematologic effects in the surviving animals.

The changes in organ weights in the 13-week studies were generally consistent with the histopathologic observations. There is no ready explanation for the decreased heart weight in chlorobenzene-treated male mice, however, or for the decreased splenic weight in all groups of chlorobenzene-treated male rats. Histological lesions of the heart were not observed, and lymphoid depletion of the spleen in male rats occurred only at the highest dose, 750 mg/kg. Yet, the decreased splenic weight in chlorobenzene-treated rats has also been reported previously (see Table 1)

The concurrent observations of proximal tubular degeneration (or necrosis) and regeneration in the kidneys of rats and mice receiving chlorobenzene for up to 90 days indicate continuing injury and repair of the renal tubular epithelium. The centrilobular hepatocellular necrosis found in both species is consistent with previous reports of chlorobenzene hepatotoxicity (see Table 1, and Introduction).

The high doses used in the 2-year studies differed from those required to produce frank tissue injury in the 13-week studies by factors of 2-4. Despite the relative closeness of the 13-week and 2-year doses, nonneoplastic lesions clearly attributable to chlorobenzene were not observed in the 2-year studies. The subtle (generally focal, and mild or minimal in severity) hepatonecrogenic lesions diagnosed by the original pathologist were not confirmed during a "blind" review of all liver slides by a second pathologist. These equivocal effects, therefore, were not considered to be clear evidence of chlorobenzene hepatotoxicity in the 2-year studies.

More striking was the general tendency for chlorobenzene-treated rats of both sexes to exhibit lower incidences of inflammatory and cytoplasmic changes in the liver (Table 7), as confirmed during the review of the liver slides. This "sparing" effect from alterations such as those that normally increase in frequency with age could not be attributed solely to reduced survival. The cause and the significance of these effects are unknown.

The failure of chlorobenzene to produce lymphoid or myeloid depletion of the bone marrow, spleen or thymus in the 2-year studies suggests that the adverse effects of this agent on the hematopoietic system in rodents are not progressive beyond 90 days of exposure. Similarly, the lack of frank nephrotoxicity or hepatotoxicity in the 2-year studies indicates little potential for chlorobenzene to produce progressive nonneoplastic toxicity more severe than that observed in the 13-week studies.

The high doses used in the 2-year studies were 120 mg/kg/day for male and female rats and female mice, and 60 mg/kg/day for male mice. These doses did not shorten group survivals, reduce body weight gains or cause nonneoplastic injury in the female rats or mice. The use of higher doses in the 2-year studies, however, was precluded by the occurrence of severe liver injury (and other tissue injuries) in male and female rats and mice at 250 mg/kg/day in the 13-week studies. Body weight gains were not depressed for

male rats in the 2-year studies, but survival was reduced in comparison to vehicle (but not in comparison to untreated) controls. Since toxic lesions were not observed in the dosed male rats dying early, the toxicological significance of the reduced survival is unknown. Of the three high dose male rats dying before week 52 of the study, one was a suspect gavage accident and the other two were severely autolyzed.

Survival was marginally reduced in the low dose (30 mg/kg/day) and high dose (60 mg/kg/day) male mice, although body weight gain was unaffected. No chlorobenzene-induced toxic lesions were observed in the dosed male mice dying early during the study. Of the four low dose male mice dying before week 52, three were moribund sacrifices without clear evidence of a toxic effect and one was severely autolyzed. Of the three high dose male mice dying before week 52, two were found dead without evidence of toxic lesions and one was severly autolyzed. Therefore, these data do not indicate that chlorobenzene administration was the likely cause of the marginally reduced survival in male mice.

Because of the lack of frank toxicity at 125 mg/kg/day in the 13-week studies, male mice may have been able to tolerate more than 60 mg/kg/day in the 2-year studies. Severe tissue injuries were present at 250 mg/kg/day in the 13-week studies, however, indicating that the 2-year dose was within a factor of 4 of a severely toxic dose. In light of the data discussed above, the high doses used in this study were considered to be adequate for carcinogenicity testing in male and female rats and mice.

Foreign body aspiration into the lung and focal granulomatous inflammation of the lung were diagnosed frequently in gavaged animals, but not in untreated controls. Presumably, therefore, these lesions could have been caused by the technique of oral intubation with corn oil. Histopathologic examinations did not indicate the nature of the foreign materials in the lung. However, the occurrence of foreign body aspirants in rats appeared to increase with the dose of chlorobenzene, even among animals that were not considered to have died from gavage accidents (Table 9). An analysis of individual animal pathology summaries, however, revealed that 1 of 14 low dose males, 1 of 8 high dose males, 4 of 5 low dose females and 3 of 7 high dose females with foreign materials in the lung died on or before the 52nd week of the study (half-way point), but were not diagnosed as accidental deaths. Therefore, aspiration of chlorobenzene-containing gavaged material may have had a greater effect on rat survival than suggested by the number of animals formally listed as dying from gavage accidents.

Inflammation of the lung diagnosed as "acute/chronic" occurred in untreated controls as well as in gavaged rats (Table 9). The frequency of this lesion appeared to increase with chlorobenzene dose, however, particularly in female rats. In contrast, focal granulomatous inflammation occurred only in gavaged rats, and at decreasing frequency with increasing chlorobenzene dose (Table 9). Although these data are far from conclusive, they seem to suggest that the gavage technique *per se* is associated with the induction of inflammatory changes in the rat lung, possibly from aspiration of the gavaged material into the lungs. The potential relationship of this gavage effect to the toxic effects elicited by chlorobenzene in this study is unknown.

Furthermore, the differential diagnoses of "inflammation, acute/chronic" and "inflammation, focal granulomatous" in the rat lung are highly subjective, and may well entail considerable overlap. When combined, the incidences of inflammation, acute/chronic, or focal granulomatous do not indicate a chlorobenzene dose-related effect (7/50, 12/50, 11/50, 5/50 in males; 2/47, 15/49, 14/49, 14/49 in females; untreated control, vehicle control, low dose and high dose, respectively). As indicated, therefore, the technique of gavage may have been associated with inflammatory changes in the lungs, particularly those of the female rats, but the data do not indicate a causative role of chlorobenzene in producing this lesion.

Chlorobenzene was associated with an increased occurrence of neoplastic nodules in the livers of male rats. Generally considered to be late-occurring lesions, the first neoplastic nodule of the liver was detected in a vehicle control male rat that died at week 89, and the majority in all groups were detected at study termination. The incidences of neoplastic nodules of the liver in male rats surviving for at least 89 weeks were 4/44 (9%), 2/48 (4%), 4/40 (10%), and 8/32 (25%) in the untreated control, vehicle control, low dose, and high dose groups, respectively. Pairwise comparisons by the Fisher exact test indicated that the incidence in high dose male rats was significantly ($P<0.05$) increased in comparison to the vehicle controls or the combined (vehicle and untreated) controls.

IV. DISCUSSION AND CONCLUSIONS

The occurrence of neoplastic nodules of the liver in the concurrent vehicle controls, 2/50 (4%), was similar to that observed in the other corn oil gavage control male rats at this laboratory (0/50, 0%) and in recent NTP studies (21/789, 2.7%, SD = 3.8%) (Appendix H, Table H1). The occurrence of neoplastic nodules of the liver in the concurrent untreated controls, 4/50 (8%), was not significantly different (i.e., $P>0.05$) from that in the concurrent vehicle controls (2/50, 4%), but was greater than that in historical untreated male rat controls for recent NTP studies (67/3618, 1.9%)*. Because of the numerical difference in the incidences in the two control groups in this study, the occurrences of neoplastic nodules in the chlorobenzene-treated male rats were compared to those in combined (untreated and vehicle) controls (Table 16). Chlorobenzene was associated with an increased occurrence of neoplastic nodules in the high dose (120 mg/kg/day) male rats in comparison to the composite control group. The increase in neoplastic nodules of the liver in male rats, therefore, was considered to be chlorobenzene-induced.

The occurrence of hepatocellular carcinomas in vehicle control male rats, 2/50 (4%), was equal to the highest rate reported for control male rats in recent NTP bioassays, and was greater than the program-wide recent historical rate for corn oil gavage male rats (7/789, 0.9%, SD = 1.6%). The reason for the relatively high incidence of hepatocellular carcinomas in vehicle control male rats in this study is unknown. Hepatocellular carcinomas were not diagnosed in untreated control or chlorobenzene-treated male rats in this study.

The incidence of animals with testicular interstitial cell tumors was increased in male rats (life table trend test) and the incidence in the high dose group was significantly ($P<0.05$) greater than that in the vehicle controls (life table analysis, Appendix I, Table I1). Because of the nonlethal nature of testicular interstitial cell tumors, however, life table tests are considered to be less appropriate for analysis of this tumor type than are the incidental tumor test or the Cochran-Armitage Trend and Fisher exact tests, none of which clearly demonstrated statistical significance ($P<0.05$). The increase by life table analysis is probably due to the number of early deaths (reduced survival) in high dose male rats. Therefore, the data were not considered as evidence of a biological effect of chlorobenzene on the testis.

Although not of statistical significance, the occurrence of a renal tubular cell adenocarcinoma in a single high dose female rat, and of transitional cell papillomas of the urinary bladder in one each of the low and high dose male rats, are of toxicologic concern because of the relative rarity of these tumors in corn oil vehicle control rats (historical incidence of 0/789 renal tubular cell adenocarcinomas in control F344 female rats; historical incidence of 0/788 transitional cell papillomas of the urinary bladder in control F344 male rats).

Pituitary adenomas in high dose (120 mg/kg/day) female rats, pituitary adenomas, adenocarcinomas or carcinomas (combined) in high dose (120 mg/kg/day) male rats, and endometrial stromal polyps in low dose (60 mg/kg/day) female rats occurred at significantly ($P<0.05$) lower incidences by at least one statistical test than in the vehicle controls. The reason for the decreased occurrences of these tumors in chlorobenzene-treated rats, and their biological significance, are unknown.

Information summarized in the Introduction indicates that chlorobenzene is oxidized to a chemically reactive intermediate (arene oxide) that can arylate nucleophilic macromolecules. These data further suggest that such an interaction, which may be the cause of liver necrosis, occurs only with chlorobenzene doses sufficent to deplete the cytosolic nucleophile glutathione below a critical level in the liver. The relationships between chlorobenzene dose, liver glutathione content, and liver necrosis or degeneration (or other tissue injuries) in these studies are unknown. While liver necrosis occurred in the 13-week studies in both species and sexes, there was only equivocal evidence for nonneoplastic injury to the liver of rats in the 2-year studies. Moreover, none of the 8 male rats in the high dose (120 mg/kg/day) group with neoplastic nodules of the liver were among the 5 animals from the same group diagnosed as having mild or focal hepatocellular necrosis by one of the

* In this statistical comparison of the incidences of neoplastic nodules of the liver in concurrent untreated control male rats and historical untreated control male rats, adjustments were not made for possible differences in survival.

TABLE 16. ANALYSIS OF LIVER TUMORS IN MALE RATS: STATISTICAL COMPARISONS OF TREATED GROUPS AND COMBINED (VEHICLE AND UNTREATED) CONTROLS

	All Controls	60 mg/kg	120 mg/kg
Neoplastic Nodule			
Tumor Rates			
Overall	6/100 (6%)	4/49 (8%)	8/49 (16%)
Adjusted	7.3%	12.5%	29.3%
Terminal	2/73 (3%)	4/32 (13%)	7/26 (27%)
Statistical Tests			
Life Table	P=0.007	P=0.378	P=0.008
Incidental Tumor Test	P=0.010	P=0.393	P=0.011
Cochran-Armitage Trend Test	P=0.034		
Fisher Exact Test		P=0.428	P=0.045
Neoplastic Nodule or Carcinoma			
Tumor Rates			
Overall	8/100 (8%)	4/49 (8%)	8/49 (16%)
Adjusted	9.9%	12.5%	29.3%
Terminal	4/73 (5%)	4/32 (13%)	7/26 (27%)
Statistical Tests			
Life Table	P=0.024	P=0.542	P=0.025
Incidental Tumor Test	P=0.032	P=0.558	P=0.032
Cochran-Armitage Trend Test	P=0.093		
Fisher Exact Test		P=0.600	P=0.106

pathologists. Therefore, there is no clear evidence to indicate that hepatonecrogenic effects of chlorobenzene contributed to the development of neoplastic nodules of the liver in these studies.

Arene oxides (epoxides) have been proposed as intermediates in the metabolism of benzene and (mono)chlorobenzene, and some similarities exist in the types of benzene and chlorobenzene metabolites excreted in urine (e.g., phenols and catechols, glucuronide and sulfate conjugates, and mercapturic acids) (Introduction to this report and IARC, 1982). In addition to possessing similar pathways of metabolism, chlorobenzene and benzene both produce hematotoxic effects in rodents, perhaps secondary to bone marrow toxicity (this report; IARC, 1982). Because of these similarities in metabolism and toxicity, speculation on the adequacy of rodent models as predictors of potential human toxic response to benzene may also be relevant to (mono)chlorobenzene. There is considerable evidence of a leukemogenic effect of benzene in exposed humans, but no clear demonstration of leukemogenic properties of benzene in experimental animals. In NTP two-year gavage studies of benzene, peer reviewed in July 1984, doses of 50, 100, or 200 mg/kg per day in male rats and 25, 50, or 100 mg/kg per day in female rats and male and female mice produced a variety of carcinogenic effects. This apparent inability to reproduce in rodent models the human response to benzene, a chemical similar to (mono)chlorobenzene in its structure and in some aspects of its metabolism and biological effects, should be considered when evaluating the results of this experiment as a predictor of the response of nonrodent species to chlorobenzene. Similarly, differences in routes of exposure (e.g., inhalation versus oral) and their potential impact on target organ toxicity should be considered in any evaluation of potential human health effects of chlorobenzene, based on these studies.

1,2-Dichlorobenzene (*o*-dichlorobenzene) and 1,4-dichlorobenzene (*p*-dichlorobenzene) have also been tested in rodents for toxic potential by the National Toxicology Program. The toxic effects of *o*- and *p*-dichlorobenzene in the 13-

week studies were virtually the same as those of (mono)chlorobenzene (NTP, 1983; J. Goldstein, NTP, personal communication; and this report). It was concluded that *o*-dichlorobenzene was not carcinogenic to male or female F344 rats or $B6C3F_1$ mice when administered for 2 years by gavage at doses of 60 or 120 mg/kg/day (NTP, 1983). The 2-year studies of *p*-dichlorobenzene in rats and mice have not been completed*.

* A final report on the carcinogenicity study of *p*-dichlorobenzene in rats and mice is expected to be peer reviewed in 1985.

Conclusions: Under the conditions of these studies, chlorobenzene administration increased the occurrence of neoplastic nodules of the liver in high dose (120 mg/kg/day) male F344/N rats, providing some but not clear evidence of carcinogenicity of chlorobenzene in male rats. Carcinogenic effects of chlorobenzene were not observed in female F344/N rats or in male or female $B6C3F_1$ mice.

V. REFERENCES

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ACGIH, American Conference of Governmental Industrial Hygienists, Threshold Limit Values, Third Edition, American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio; 1979, p. 79.

Ames Co., Operating manual hema-tek slide staining stain pak. Elkart, Indiana; Ames Co., Division of Miles Laboratory, 1974.

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

Armitage, P., Statistical methods in medical research. New York: John Wiley & Sons, Inc.; 1971:362-365.

Ariyoshi, T.; Ideyuchi, K.; Ishizuka, Y.; Iwasaki, K.; Arakaki, M., Relationship between chemical structure and activity. I. Effects of the number of chlorine atoms on chlorinated benzenes on the components of the drug metabolizing system and the hepatic constituents. Chem. Pharmaceut. Bull. 23:817-823; 1975.

Azouz, W.; Parke, D.; Williams, R., Studies in detoxification. Fluoronitrobenzene. J. Biochem. 50:702-706; 1950.

Berenblum, I., ed., Carcinogenicity testing: a report of the panel on carcinogenicity of the cancer research commission of UICC. Geneva: International Union Against Cancer, Vol. 2; 1969.

Brodie, B.; Reid, W.; Cho, A.; Sipes, G.; Krishna, G.; Gillette, J., Possible mechanism of liver necrosis caused by aromatic organic compounds. Proc. Nat. Acad. Sci. 68:150-164; 1971.

Cameron, G.; Thomas, J.; Ashmore, S.; Buchan, A.; Warren, E.; McKenny-Hughes, A., The toxicities of certain chlorinated derivatives of benzene with special reference to *o*-dichlorobenze. J. Pathol. Bacteriol. 44:281-296; 1933.

Carlson, G.; Tardiff, R., Effect of chlorinated benzenes on the metabolism of foreign organic compounds. Toxicol. Appl. Pharmacol. 36: 383-394; 1976.

Cox, D.R., Regression models and life tables. J.R. Stat. Soc. B34; 187-220; 1972.

Deichmann, W., Halogenated cyclic hydrocarbons. In: Patty's industrial hygiene and toxicology, 3rd ed. New York: John Wiley and Sons, Vol 2B; 1981:3603-3611.

Dowty, B.; Carlisle, D.; Laseter, J., New Orleans drinking water sources tested by gas chromatography mass spectrometry: occurrence and origin of aromatics and halogenated aliphatic hydrocarbons. Environ. Sci. Tech. 9:762-765;1975.

Fishbein, L., Potential halogenated industrial carcinogenic and mutagenic chemicals IV. Halogenated aryl derivatives. Sci. Total Environ. 11:259-278; 1979.

Gart, J.; Chu, K.; Tarone, R., Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974; 1979.

Gillham, B.; Young, L., Biochemical studies of toxic agents. The isolation of premercapturic acids from the urine of animals dosed with chlorobenzene and bromobenzene. J. Biochem. 109:143-147; 1968.

Hayes, W.; Gushow, T.; Johnson, K.; Hanley, T.; Ouellette, J.; John, J., Monochlorobenzene—Inhalation teratology study in rats and rabbits. Midland, MI: Dow Chemical Company, 1982.

IARC, IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 29. Some industrial chemicals and dyestuffs. Lyon, France: International Agency for Research on Cancer, 1982: 95-148.

Jollow, D.J.; Smith, C., Biochemical aspects of toxic metabolites. Formation, detoxication and covalent binding. In: Biological Reactive Intermediates; eds., D.J. Jollow, J.J. Kocsis, R. Snyder, and H. Vainio, New York: Plenum Press; 1977:42-59.

Kaplan, E.L.; Meier, P., Nonparametric estimation of incomplete observations. J. Amer. Stat. Assoc. 53:457-481; 1958.

Keskinova, D., The action of dimethylcyclodiazomethane in chlorobenzene solutions on the mutation process in *Actinomycetes antibioticus*-400. Sov. Gen. 4:1082-1085; 1968.

Kirk-Othmer encyclopedia of chemical technology. Vol. 5, New York: Interscience Publishers; 1964:253.

Knapp, W.; Busey, W.; Kundzins, W., Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19:393(A); 1971.

V. REFERENCES

Lavallee, D.K.; Norelius, J.T., Compensation by zinc chelation for fluorescent background in determining coproporphyrin and uroporphyrin in urine. Clin. Chem. (Winston-Salem, N.C.). 23(2 Pt. I):282-285; 1977.

Lawlor, T.; Hanworth, S.; Voytek, P., Evaluation of the genetic activities of nine chlorinated phenols, seven chlorinated benzenes and three chlorinated hexanes. Environ. Mutagen. 1:143 (A); 1979.

Linhart, M.S.; Cooper, J.A.; Martin, R.L.; Page, N.P.; Peters, J.A., Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248; 1974.

Lynch, M.J.; Rapheal, S.S.; Mellor, L.D.; Spare, P.D.; Inwood, M.J., Medical laboratory technology and clinical pathology, 2nd ed., Philadelphia: W.B. Saunders Co., 1969:1359.

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

Maronpot, R.R.; Boorman, G.A., Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10(2):71-80; 1982.

Merck Index, 8th ed., Rahway, New Jersey: Merck and Co., 1968:240; 1976: 2098.

Miale, G., Laboratory medicine hematology, 3rd ed., St. Louis: C.V. Mosby Co., 1967:1257.

Miller, R., Jr., Simultaneous statistical inference, New York, Springer-Verlag, Inc., 1981:76-81.

National Academy of Sciences. Histologic typing of liver tumors of the rat. J. Natl. Cancer Inst. 64:179-206; 1980.

NIOSH, National Institute for Occupational Safety and Health, Extent-of-exposure survey of monochlorobenzene. DHHS Pub. No. (NIOSH) 81-105, NIOSH, Cincinnati, OH: Division of Surveillance, Hazard Evaluation and Field Studies, 1981.

NIOSH, National Institute for Occupational Safety and Health, Toxicology evaluation of inhaled chlorobenzene (monochlorobenzene). NTIS PB-276-623, NIOSH, Cincinnati, OH: Division of Biomedical and Behavioral Sciences, 1977.

NTP, National Toxicology Program, Environmental Mutagen Test Development Program, Research Triangle Park, NC, 1982.

NTP, National Toxicology Program, NTP Technical Report on the carcinogenesis bioassay of 1,2-dichlorobenzene in F344 rats and B6C3F$_1$ mice. NTP TR 255, U.S. Dept. of Health and Human Services, Research Triangle Park, North Carolina, 1983.

Parke, D.; Williams, R., Studies in detoxification. 63. The metabolism of halogenobenzenes. J. Biochem. 59:415-422; 1955.

Peto, R.; Pike, M.; Day, N.; Gray, R.; Lee, R.; Parish, S.; Peto, J.; Richard, S.; Wahrendorf, J., Guidelines for simple, sensitive, significant tests for carcinogenic effects in long-term animal experiments. International Agency for Research Against Cancer. Monographs on the long-term and short-term screening assays for carcinogens: A critical appraisal. Geneva: World Health Organization. Supplement 2; 1980:311.

Reid, W., Mechanism of renal necrosis induced by bromobenzene or chlorobenzene. Exp. Molec. Pathol. 19:197-214; 1973.

Reid, W.; Ilett, K.; Glick, J.; Krishna, G., Metabolism and binding of aromatic hydrocarbons in the lung. Relationship to experimental bronchiolar necrosis. Ann. Rev. Resp. Dis. 107:539-551; 1973.

Rimington, C.; Ziegler, G., Experimental porphyria in rats induced by chlorinated benzenes. Biochem. Pharmacol. 12:1387-1397; 1963.

Sadtler Research Laboratories. Sadtler standard spectra. Philadelphia: Sadtler Research Laboratories; IR No. 34; UV No. 16; NMR No. 714.

Smith, J.; Spencer, B.; Williams, R., Studies in detoxication. 30. The metabolism of chlorobenzene in the rabbit. J. Biochem. 47:284-293; 1950.

Smith, J.; Shaw, B.; Foulkes, D., Mechanisms of mammalian hydroxylation: some novel metabolites of chlorobenzene. Xenobiotica 2:215-226; 1972.

Sobel, C.; Cano, C.; Thiers, R.E., Separation and quantitation of coproporphyrin and uroporphyrin in urine. Clin. Chem. 20(11):1397-1402; 1974.

Squire, R.; Levitt, M., Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35 (11 Pt 1):3214-3223; 1975.

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

V. REFERENCES

USITC, United States International Trade Commission, Synthetic Organic Chemicals, United States Production and Sales 1980. USITC Publication 1189, U.S. Government Printing Office, Washington, D.C., 1981.

Varshavskaya, S., Comparative toxicologic features of chlorobenzene and dichlorobenzene (ortho and para isomers) in sanitary protection of water bodies. Hygiene and Sanitation 33:17-23; 1967.

Ward, J.; Goodman, D.; Griesemer, R.; Hardisty, J.; Schueler, R.; Squire, R.; Strandberg, J., Quality assurance for pathology in rodent carcinogenesis tests. J. Environ. Path. Toxicol. 2:371-378; 1978.

Yahagi, T.; Degawa, M.; Seino, Y.; Matsushima, T.; Nagao, M.; Sugimura, P.; Hashimoto, Y., Mutagenicity of carcinogenic azo dyes and their derivatives, Cancer Lett., 1:91-96;1975.

Zub, M., Reactivity of the white blood cell system to toxic actions of benzene and its derivatives. Acta. Biol. Cracoviensia 21:163-174; 1978.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			2 (4%)	
SQUAMOUS CELL CARCINOMA		1 (2%)		
BASAL-CELL CARCINOMA	1 (2%)	1 (2%)		1 (2%)
KERATOACANTHOMA	2 (4%)		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FIBROMA	4 (8%)	5 (10%)	2 (4%)	2 (4%)
FIBROSARCOMA		2 (4%)		1 (2%)
OSTEOSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)			
FIBROSARCOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)			
LEUKEMIA,NOS	4 (8%)			
UNDIFFERENTIATED LEUKEMIA	3 (6%)	1 (2%)	2 (4%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)		
GRANULOCYTIC LEUKEMIA		1 (2%)		
LEUKEMIA,MONONUCLEAR CELL	12 (24%)	4 (8%)	9 (18%)	3 (6%)
#LIVER	(50)	(50)	(49)	(49)
LEUKEMIA,MONONUCLEAR CELL		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
#SPLEEN	(48)	(50)	(49)	(47)
HEMANGIOMA				1 (2%)
#TESTIS	(50)	(50)	(49)	(50)
HEMANGIOSARCOMA				1 (2%)
DIGESTIVE SYSTEM				
*LIP	(50)	(50)	(50)	(50)
KERATOACANTHOMA				1 (2%)
*DORSUM OF TONGUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	1 (2%)
#LIVER	(50)	(50)	(49)	(49)
NEOPLASTIC NODULE	4 (8%)	2 (4%)	4 (8%)	8 (16%)
HEPATOCELLULAR CARCINOMA		2 (4%)		
#PANCREAS	(48)	(50)	(48)	(48)
ACINAR-CELL ADENOMA			1 (2%)	1 (2%)
MIXED TUMOR, MALIGNANT	1 (2%)			
#ESOPHAGUS	(50)	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		
#CARDIAC STOMACH	(48)	(50)	(49)	(48)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
#DUODENAL MUCOSA	(46)	(50)	(47)	(46)
ADENOCARCINOMA, NOS			1 (2%)	
URINARY SYSTEM				
#URINARY BLADDER	(48)	(48)	(46)	(45)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(50)	(42)	(47)
CARCINOMA,NOS		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ADENOMA, NOS	20 (41%)	10 (20%)	9 (21%)	3 (6%)
#ANTERIOR PITUITARY	(49)	(50)	(42)	(47)
ADENOCARCINOMA, NOS		1 (2%)		
#ADRENAL	(49)	(49)	(49)	(49)
PHEOCHROMOCYTOMA	10 (20%)	11 (22%)	7 (14%)	5 (10%)
#ADRENAL MEDULLA	(49)	(49)	(49)	(49)
GANGLIONEUROMA				1 (2%)
#THYROID	(49)	(50)	(49)	(43)
FOLLICULAR-CELL CARCINOMA		1 (2%)		
C-CELL CARCINOMA	6 (12%)	6 (12%)	5 (10%)	3 (7%)
PAPILLARY CYSTADENOMA, NOS	1 (2%)			1 (2%)
#THYROID FOLLICLE	(49)	(50)	(49)	(43)
CYSTADENOMA, NOS		1 (2%)	2 (4%)	
CYSTADENOCARCINOMA, NOS			1 (2%)	
#PANCREATIC ISLETS	(48)	(50)	(48)	(48)
ISLET-CELL ADENOMA			1 (2%)	
ISLET-CELL CARCINOMA	3 (6%)	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
FIBROADENOMA	3 (6%)	2 (4%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA,NOS			1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
PAPILLARY ADENOMA		1 (2%)		
#TESTIS	(50)	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR	47 (94%)	44 (88%)	43 (88%)	43 (86%)
INTERSTITIAL-CELL TUMOR, MALIGNA		1 (2%)		
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
GRANULAR-CELL TUMOR, BENIGN	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#BRAIN	(50)	(50)	(50)	(50)
ASTROCYTOMA			1 (2%)	
#HIPPOCAMPUS	(50)	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)			
#CINGULUM	(50)	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)			
*LUMBAR SPINAL CORD	(50)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*EYELID	(50)	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)	
*ZYMBAL'S GLAND	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS		3 (6%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS				1 (2%)
MESOTHELIOMA, MALIGNANT	1 (2%)			1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
ADIPOSE TISSUE				
MESOTHELIOMA, NOS		1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	7	3	7	8
MORIBUND SACRIFICE	9	6	5	7
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	34	39	32	26
DOSING ACCIDENT		1	4	5
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS		1	2	4
ANIMAL MISSING				
ANIMAL MISSEXED				
OTHER CASES				

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	49	46	43
TOTAL PRIMARY TUMORS	128	108	101	84
TOTAL ANIMALS WITH BENIGN TUMORS	50	48	45	43
TOTAL BENIGN TUMORS	88	75	71	61
TOTAL ANIMALS WITH MALIGNANT TUMORS	30	21	21	12
TOTAL MALIGNANT TUMORS	36	27	25	13
TOTAL ANIMALS WITH SECONDARY TUMORS#		2	1	
TOTAL SECONDARY TUMORS		2	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	4	5	5	10
TOTAL UNCERTAIN TUMORS	4	6	5	10
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA				1 (2%)
KERATOACANTHOMA			1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)			
LIPOSARCOMA			1 (2%)	
NEUROFIBROSARCOMA	1 (2%)	1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
LIPOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
LEUKEMIA,NOS	2 (4%)		1 (2%)	
UNDIFFERENTIATED LEUKEMIA		3 (6%)	1 (2%)	
LYMPHOCYTIC LEUKEMIA	4 (8%)			
LEUKEMIA,MONONUCLEAR CELL	3 (6%)	5 (10%)	8 (16%)	11 (22%)
#PANCREATIC L.NODE	(47)	(45)	(40)	(40)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*DORSUM OF TONGUE	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
#SALIVARY GLAND	(49)	(50)	(49)	(49)
ADENOMA, NOS		1 (2%)		
#LIVER	(49)	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)		1 (2%)	1 (2%)
HEPATOCELLULAR CARCINOMA				1 (2%)
#PANCREAS	(46)	(50)	(49)	(49)
ACINAR-CELL ADENOMA			1 (2%)	
#GASTRIC MUSCULARIS	(49)	(50)	(49)	(50)
LEIOMYOMA				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(48)	(46)	(46)	(43)
CARCINOMA,NOS	1 (2%)		1 (2%)	
ADENOMA, NOS	27 (56%)	23 (50%)	18 (39%)	13 (30%)
#ANTERIOR PITUITARY	(48)	(46)	(46)	(43)
ADENOCARCINOMA, NOS			1 (2%)	
ASTROCYTOMA, INVASIVE				1 (2%)
#ADRENAL	(49)	(49)	(49)	(49)
CORTICAL ADENOMA	1 (2%)			1 (2%)
CORTICAL CARCINOMA		1 (2%)		
PHEOCHROMOCYTOMA	3 (6%)	1 (2%)	4 (8%)	2 (4%)
#THYROID	(49)	(49)	(49)	(49)
FOLLICULAR-CELL CARCINOMA			1 (2%)	2 (4%)
C-CELL CARCINOMA	3 (6%)	4 (8%)	1 (2%)	1 (2%)
PAPILLARY CYSTADENOMA, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID FOLLICLE	(49)	(49)	(49)	(49)
CYSTADENOMA, NOS			1 (2%)	
#PARATHYROID	(37)	(40)	(32)	(38)
ADENOMA, NOS				1 (3%)
#PANCREATIC ISLETS	(46)	(50)	(49)	(49)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)	
ISLET-CELL CARCINOMA		1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
ADENOMA, NOS			1 (2%)	
PAPILLARY ADENOMA		1 (2%)		
PAPILLARY ADENOCARCINOMA	1 (2%)			
CYSTADENOMA, NOS	1 (2%)	1 (2%)		
PAPILLARY CYSTADENOMA, NOS	1 (2%)		1 (2%)	
FIBROADENOMA	7 (14%)	7 (14%)	5 (10%)	7 (14%)
FIBROADENOCARCINOMA				1 (2%)
*CLITORAL GLAND	(49)	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)	1 (2%)
#UTERUS	(49)	(50)	(49)	(50)
SARCOMA, NOS				1 (2%)
LEIOMYOMA				1 (2%)
ENDOMETRIAL STROMAL POLYP	9 (18%)	16 (32%)	4 (8%)	10 (20%)
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)	(50)
CARCINOSARCOMA				1 (2%)
#ENDOMETRIAL GLAND	(49)	(50)	(49)	(50)
ADENOMA, NOS	1 (2%)			
#OVARY	(49)	(50)	(49)	(50)
PAPILLARY CYSTADENOMA, NOS		1 (2%)		
LUTEOMA	1 (2%)		1 (2%)	
GRANULOSA-CELL TUMOR	2 (4%)	2 (4%)	1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM				
#CEREBRUM	(49)	(50)	(50)	(50)
ASTROCYTOMA				1 (2%)
#BRAIN	(49)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		1 (2%)	
#CEREBELLUM	(49)	(50)	(50)	(50)
GRANULAR-CELL TUMOR, BENIGN		1 (2%)		
SPECIAL SENSE ORGANS				
*EAR	(49)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		
*EXTERNAL EAR	(49)	(50)	(50)	(50)
NEUROFIBROSARCOMA	1 (2%)			
*ZYMBAL'S GLAND	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	5	5	5	4
MORIBUND SACRIFICE	8	8	6	8
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	36	29	30	31
DOSING ACCIDENT		1	5	5
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS		7	4	2
ANIMAL MISSING	1			
ANIMAL MISSEXED				
OTHER CASES				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	42	36	30	36
TOTAL PRIMARY TUMORS	72	72	57	63
TOTAL ANIMALS WITH BENIGN TUMORS	35	34	27	23
TOTAL BENIGN TUMORS	52	52	39	38
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	16	14	21
TOTAL MALIGNANT TUMORS	17	18	16	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	2		1	1
TOTAL SECONDARY TUMORS	2		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	2	2	2
TOTAL UNCERTAIN TUMORS	3	2	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	041	041	071	041	011	041	098	041	045	085	086	041	041	041	041	041	075	041	041	041	041	041	041	041	041
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
BASAL-CELL CARCINOMA																									
KERATOACANTHOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
FIBROMA						X																			
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+
THYMUS	+	-	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																						X	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	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED TUMOR, MALIGNANT																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS			X	X	X	X	X	X						X		X		X	X				X		X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X	X				X						X	X			X							
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA														X								X			
PAPILLARY CYSTADENOMA, NOS																									
PARATHYROID	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA									X																X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	N	+	N	N	N	N	N	N	+	N	+	+	N	N	N	N	+	N	N	N	+
FIBROADENOMA						X										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	X
PROSTATE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULAR-CELL TUMOR, BENIGN																									
ASTROCYTOMA				X														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
MESOTHELIOMA, MALIGNANT																									
MALIG.LYMPHOMA, UNDIFFER-TYPE																									
LEUKEMIA,NOS			X																						
UNDIFFERENTIATED LEUKEMIA																									
LEUKEMIA,MONONUCLEAR CELL					X	X	X									X		X					X	X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) UNTREATED CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	084	104	104	102	104	094	091	072	104	098	104	096	099	104	088	104	104	104	104	104	101	095	104	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50M
BASAL-CELL CARCINOMA																X										1
KERATOACANTHOMA																				X	X					2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50M
FIBROMA																X			X			X				4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA					X																			X		2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LYMPH NODES	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	43
THYMUS	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE									X															X		4
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	50M
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MIXED TUMOR, MALIGNANT														X												1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	49
ADENOMA, NOS			X		X							X				X	X					X	X	X		20
ADRENAL	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA						X												X			X	X				10
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL CARCINOMA						X			X									X					X			6
PAPILLARY CYSTADENOMA, NOS						X																				1
PARATHYROID	+	-	-	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	41
PANCREATIC ISLETS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL CARCINOMA																									X	3
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	N	+	N	N	N	N	+	+	+	+	N	N	+	+	N	+	N	N	+	+	+	+	50M
FIBROADENOMA											X															3
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	47
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULAR-CELL TUMOR, BENIGN																									X	1
ASTROCYTOMA																										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	50M
MESOTHELIOMA, MALIGNANT										X																1
MALIG.LYMPHOMA, UNDIFFER-TYPE															X											1
LEUKEMIA,NOS												X				X		X								4
UNDIFFERENTIATED LEUKEMIA								X	X								X									3
LEUKEMIA,MONONUCLEAR CELL		X		X	X	X	X																			12

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	099	064	104	104	104	104	091	084	089	104	104	092	105	083	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																					X				
BASAL-CELL CARCINOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
FIBROMA									X																X
FIBROSARCOMA								X														X			
OSTEOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
HEPATOCELLULAR CARCINOMA, METASTA																								X	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	-	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	-	+	+	-
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
HEPATOCELLULAR CARCINOMA																		X						X	
LEUKEMIA,MONONUCLEAR CELL		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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS	X	X		X							X		X			X		X						X	
ADENOCARCINOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X												X	X		X			X				X	X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL CARCINOMA												X		X										X	
CYSTADENOMA, NOS																									
PARATHYROID	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	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		X	X	X	X	X		X
INTERSTITIAL-CELL TUMOR, MALIGNAN																									
PROSTATE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SEMINAL VESICLE	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS											X												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
UNDIFFERENTIATED LEUKEMIA															X										
LYMPHOCYTIC LEUKEMIA																									
GRANULOCYTIC LEUKEMIA																									
LEUKEMIA,MONONUCLEAR CELL									X									X							
ADIPOSE TISSUE																									
MESOTHELIOMA, NOS																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 42	04 43	04 46	04 45	04 46	04 47	04 48	04 49	05 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 04	08 89	10 04	11 04	10 04	10 04	10 04	10 01	10 04	10 04	10 04	10 04	10 04	10 04	08 91	10 04	10 04	09 96	10 01	10 04	10 04	10 04	10 04	10 04	
INTEGUMENTARY SYSTEM																									
SKIN	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50M
SQUAMOUS CELL CARCINOMA															X										1
BASAL-CELL CARCINOMA																									1
SUBCUTANEOUS TISSUE	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50M
FIBROMA			X													X		X							5
FIBROSARCOMA															X										2
OSTEOSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT															X										1
HEPATOCELLULAR CARCINOMA, METASTA																									1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	38
THYMUS	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE															X					X					2
HEPATOCELLULAR CARCINOMA																									2
LEUKEMIA,MONONUCLEAR CELL																									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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA	X																								1
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA			X																						1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																			X						1
ADENOMA, NOS										X											X				10
ADENOCARCINOMA, NOS							X																		1
ADRENAL	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA									X						X				X		X				11
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA																									1
C-CELL CARCINOMA									X		X											X			6
CYSTADENOMA, NOS			X																						1
PARATHYROID	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	-	39
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA			X																						1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	+	N	+	+	N	+	N	+	+	+	N	N	N	+	N	N	N	N	+	+	N	N	50M
FIBROADENOMA			X																						2
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	44
INTERSTITIAL-CELL TUMOR, MALIGNAN																X									1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
SEMINAL VESICLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
PAPILLARY ADENOMA																X									1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
MESOTHELIOMA, NOS										X															3
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	50M
UNDIFFERENTIATED LEUKEMIA										X															1
LYMPHOCYTIC LEUKEMIA									X																1
GRANULOCYTIC LEUKEMIA																									1
LEUKEMIA,MONONUCLEAR CELL			X																X						4
ADIPOSE TISSUE																									
MESOTHELIOMA, NOS										X															1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	105	104	104	094	104	104	101	104	100	104	104	078	081	076	104	104	104	102	080	104	095	104	068	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
SQUAMOUS CELL PAPILLOMA									X											X					
KERATOACANTHOMA		X																							
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
FIBROMA		X						X																	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA		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	
SQUAMOUS CELL PAPILLOMA								X																	
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
NEOPLASTIC NODULE																	X				X				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	
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ACINAR-CELL ADENOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	
TRANSITIONAL-CELL PAPILLOMA												X													
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	
ADENOMA, NOS											X						X	X				X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
PHEOCHROMOCYTOMA																X	X				X	X			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-CELL CARCINOMA			X																			X			
CYSTADENOMA, NOS												X													
CYSTADENOCARCINOMA, NOS																X									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	-	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ISLET-CELL ADENOMA																									
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	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		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																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA										X															
SPINAL CORD	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										
SPECIAL SENSE ORGANS																									
EYE APPENDAGES	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																									
BODY CAVITIES																									
PERITONEUM	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																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
MESOTHELIOMA, NOS																		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
OSTEOSARCOMA, METASTATIC															X										
UNDIFFERENTIATED LEUKEMIA														X											
LEUKEMIA,MONONUCLEAR CELL			X					X				X								X				X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	104	104	104	091	098	104	064	051	104	104	099	104	104	104	104	041	091	104	104	104	096	104	100	104	025	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										2
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROSARCOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	+	+	43
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	43
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																										1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE									X																	4
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														1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS									X																	1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	46
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	-	42
ADENOMA, NOS					X			X		X									X		X					9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA	X											X			X											7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
C-CELL CARCINOMA						X							X						X							5
CYSTADENOMA, NOS												X														2
CYSTADENOCARCINOMA, NOS																										1
PARATHYROID	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	-	-	+	+	+	-	+	+	+	41
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	48
ISLET-CELL ADENOMA																						X				1
ISLET-CELL CARCINOMA						X																				1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	N	+		50
FIBROADENOMA																			X							1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X		X	X	X		43
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	50
CARCINOMA,NOS																				X						1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																										1
SPINAL CORD	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
SPECIAL SENSE ORGANS																										
EYE APPENDAGES	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							X																			1
BODY CAVITIES																										
PERITONEUM	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			X																							1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50
MESOTHELIOMA, NOS																										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
OSTEOSARCOMA, METASTATIC																										1
UNDIFFERENTIATED LEUKEMIA					X	X					X									X		X				2
LEUKEMIA,MONONUCLEAR CELL																										9

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
$: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	088	093	087	041	103	087	110	041	094	072	093	083	094	041	041	091	053	068	088	041	091	024	083	041	104
INTEGUMENTARY SYSTEM																									
SKIN	+	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL CARCINOMA				X																					
SUBCUTANEOUS TISSUE	+	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA											X														
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
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																				
KERATOACANTHOMA															X										
SALIVARY GLAND	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE														X	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	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA																									
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS						X																		X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																									
GANGLIONEUROMA																									
THYROID	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
C-CELL CARCINOMA								X											X						
PAPILLARY CYSTADENOMA, NOS																									
PARATHYROID	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	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	X	X	X	X	X	X
HEMANGIOSARCOMA										X															
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
ZYMBAL'S 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
SQUAMOUS CELL CARCINOMA			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
MESOTHELIOMA, NOS					X																				
MESOTHELIOMA, MALIGNANT						X									X										
UNDIFFERENTIATED LEUKEMIA				X								X													
LEUKEMIA,MONONUCLEAR CELL																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
!: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	089	104	041	044	044	093	085	044	091	106	041	044	044	052	041	044	023	090	041	037	044	029	041	044	078	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50M
BASAL-CELL CARCINOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50M
FIBROMA							X				X															2
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	47
HEMANGIOMA	X																									1
LYMPH NODES	+	+	+	+	-	-	+	+	+	-	+	-	+	+	-	-	+	+	+	-	+	+	+	+	-	37
THYMUS	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	41
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	50M
SQUAMOUS CELL PAPILLOMA																										1
KERATOACANTHOMA																										1
SALIVARY GLAND	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	45
LIVER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE		X	X					X	X						X	X										8
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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ACINAR-CELL ADENOMA																							X			1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
LARGE INTESTINE	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
TRANSITIONAL-CELL PAPILLOMA	X																									1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS																			X							3
ADRENAL	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA		X	X																		X		X	X		5
GANGLIONEUROMA																								X		1
THYROID	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	43
C-CELL CARCINOMA								X																		3
PAPILLARY CYSTADENOMA, NOS					X																					1
PARATHYROID	+	+	+	+	-	-	+	-	+	+	+	+	-	+	-	+	+	+	+	-	+	+	+	+	+	40
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ISLET-CELL CARCINOMA			X																							1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	+	N	N	N	+	N	N	+	+	N	N	N	N	+	N	N	+	+	N	+	50M
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	43
HEMANGIOSARCOMA																										1
PROSTATE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
ZYMBAL'S 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	50M
SQUAMOUS CELL CARCINOMA																										1
BODY CAVITIES																										
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
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	50M
MESOTHELIOMA, NOS																										1
MESOTHELIOMA, MALIGNANT																										1
UNDIFFERENTIATED LEUKEMIA																										1
LEUKEMIA,MONONUCLEAR CELL									X																	3

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	101	084	103	104	104	104	104	104	089	104	104	104	105	104	104	096	104	104	104	104	104	104	104	104	084
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
NEUROFIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOSARCOMA, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	M	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	M	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS									X																
ADENOMA, NOS	X	X	X	X	X		X	X						X			X	X		X	X			X	X
ADRENAL	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA																	X							X	
THYROID	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA																			X						
PARATHYROID	+	-	+	+	+	-	+	-	M	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	N	N	+	M	+	+	N	+	N	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOCARCINOMA																									
CYSTADENOMA, NOS																									
PAPILLARY CYSTADENOMA, NOS		X																							
FIBROADENOMA														X								X		X	X
UTERUS	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
ENDOMETRIAL STROMAL POLYP					X	X								X		X		X					X		
OVARY	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LUTEOMA				X																					
GRANULOSA-CELL TUMOR																				X					
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE									X																
SPECIAL SENSE ORGANS																									
EAR	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEUROFIBROSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LEUKEMIA,NOS																X									
LYMPHOCYTIC LEUKEMIA																				X					
LEUKEMIA,MONONUCLEAR CELL								X											X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) UNTREATED CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	088	076	104	104	067	104	104	104	104	104	104	084	104	104	104	104	104	095	104	087	104	085	104	104	104	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
FIBROSARCOMA																							X			1
NEUROFIBROSARCOMA																					X					1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIPOSARCOMA, METASTATIC																		X								1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	46
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE													X													1
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	49*
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	45
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA,NOS																										1
ADENOMA, NOS			X	X		X	X		X	X	X	X				X		X	X			X		X		27
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA																								X		1
PHEOCHROMOCYTOMA						X																				3
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL CARCINOMA															X				X							3
PARATHYROID	-	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	37
PANCREATIC ISLETS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
ISLET-CELL ADENOMA								X																		1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	49*
PAPILLARY ADENOCARCINOMA													X													1
CYSTADENOMA, NOS	X																									1
PAPILLARY CYSTADENOMA, NOS																										1
FIBROADENOMA						X							X							X						7
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS												X														1
ENDOMETRIAL STROMAL POLYP				X					X											X						9
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LUTEOMA																										1
GRANULOSA-CELL TUMOR																X										2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS, INVASIVE																										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	49*
NEUROFIBROSARCOMA					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	49*
LEUKEMIA,NOS	X																									2
LYMPHOCYTIC LEUKEMIA										X	X		X													4
LEUKEMIA,MONONUCLEAR CELL		X																								3

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	029	104	099	065	104	104	104	029	099	029	083	081	104	104	044	104	026	104	028	029	088	104	104	044
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
NEUROFIBROSARCOMA														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X																		
THYMUS	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																	X								
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS			X					X		X		X	X	X			X		X			X	X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL CARCINOMA					X																				
PHEOCHROMOCYTOMA																									
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA								X											X						
PARATHYROID	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA																	X								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA																				X					
CYSTADENOMA, NOS								X																	
FIBROADENOMA				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
CARCINOMA,NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP							X			X				X	X		X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
GRANULOSA-CELL TUMOR			X											X											
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULAR-CELL TUMOR, BENIGN																			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
UNDIFFERENTIATED LEUKEMIA																						X			
LEUKEMIA,MONONUCLEAR CELL			X		X			X		X															

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	101	104	104	029	104	104	029	086	078	104	104	102	104	104	104	104	104	104	104	084	104	104	104	104	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
NEUROFIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	45
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
THYMUS	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																										1
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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
ADENOMA, NOS		X		X		X	X				X	X	X	X		X		X			X	X				23
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
CORTICAL CARCINOMA																										1
PHEOCHROMOCYTOMA							X																			1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL CARCINOMA						X						X														4
PARATHYROID	+	-	-	+	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	40
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	50M
PAPILLARY ADENOMA																										1
CYSTADENOMA, NOS																										1
FIBROADENOMA	X													X	X						X			X		7
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	50M
CARCINOMA,NOS		X																								1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP				X		X			X			X		X		X	X		X	X	X			X		16
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PAPILLARY CYSTADENOMA, NOS																			X							1
GRANULOSA-CELL TUMOR																										2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULAR-CELL TUMOR, BENIGN																										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	50M
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	50M
UNDIFFERENTIATED LEUKEMIA															X				X							3
LEUKEMIA,MONONUCLEAR CELL																							X			5

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
A: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: *NECROPSY, NO HISTOLOGY DUE TO PROTOCOL*
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	076	104	087	088	104	104	104	095	107	104	104	025	086	096	094	104	104	029	090	104	104	104	104	104	092
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA								X																	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																						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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																						X			
ADENOMA, NOS		X				X		X			X						X				X		X	X	
ADENOCARCINOMA, NOS																							X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA								X															X		
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL CARCINOMA																									
CYSTADENOMA, NOS																									
PARATHYROID	-	+	+	-	+	-	+	+	-	+	+	+	-	-	+	+	+	-	+	+	+	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	N	+	+	N	N	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																						X			
PAPILLARY CYSTADENOMA, NOS																									
FIBROADENOMA			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
ADENOCARCINOMA, NOS										X															
UTERUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP										X												X		X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LUTEOMA																									
GRANULOSA-CELL TUMOR																							X		
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																						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,NOS																									
UNDIFFERENTIATED LEUKEMIA																									
LEUKEMIA,MONONUCLEAR CELL			X		X			X							X								X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	026	104	104	076	104	104	078	027	105	029	021	105	105	029	041	072	104	104	102	104	104	104	104	104	029	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	50
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	50
LIPOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	40
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																										1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CARCINOMA,NOS																										1
ADENOMA, NOS			X	X								X				X		X	X	X	X		X			18
ADENOCARCINOMA, NOS																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA			X											X												4
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																				X						1
C-CELL CARCINOMA				X																						1
CYSTADENOMA, NOS																					X					1
PARATHYROID	-	+	-	-	+	-	+	+	-	+	+	-	-	+	-	+	-	+	-	+	+	+	+	+	+	32
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																						X				1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	N	50
ADENOMA, NOS																										1
PAPILLARY CYSTADENOMA, NOS										X																1
FIBROADENOMA								X								X			X			X			5
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
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP										X																4
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LUTEOMA			X																							1
GRANULOSA-CELL TUMOR																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE																										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,NOS																	X									1
UNDIFFERENTIATED LEUKEMIA								X																		1
LEUKEMIA,MONONUCLEAR CELL												X		X						X						8

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: *NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION*
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR STUDY OF CHLOROBENZENE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	075	104	104	029	010	026	104	029	041	006	104	104	041	104	025	104	104	104	098	080
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	-	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
THYMUS	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																		X							
HEPATOCELLULAR CARCINOMA																			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOMA																								X	
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+
ADENOMA, NOS		X						X								X					X				X
ASTROCYTOMA, INVASIVE																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA								X																	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA							X																		
C-CELL CARCINOMA			X																						
PAPILLARY CYSTADENOMA, NOS																									
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
ADENOMA, NOS	X																								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+
FIBROADENOMA		X															X					X		
FIBROADENOCARCINOMA																						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
ADENOCARCINOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS														X											
LEIOMYOMA														X											
ENDOMETRIAL STROMAL POLYP													X												X
CARCINOSARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
SPECIAL SENSE ORGANS																									
ZYMBAL'S 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
ADENOCARCINOMA, 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	X								X		X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
$: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	086	104	104	104	011	104	006	091	084	094	006	104	104	084	084	104	004	104	104	004	004	004	004	025	088	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	50*
SQUAMOUS CELL PAPILLOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																			1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	48
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
HEPATOCELLULAR CARCINOMA																										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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																		X								1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	43
ADENOMA, NOS		X				X				X	X						X	X			X	X				13
ASTROCYTOMA, INVASIVE	X																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
CORTICAL ADENOMA																						X				1
PHEOCHROMOCYTOMA				X																						2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
FOLLICULAR-CELL CARCINOMA																			X							2
C-CELL CARCINOMA																										1
PAPILLARY CYSTADENOMA, NOS				X																						1
PARATHYROID	+	+	-	-	-	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	-	+	-	+	-	38
ADENOMA, NOS																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	N	+	+	+	N	+	N	+	+	+	N	N	+	+	+	+	+	+	+	N	N	+	50*
FIBROADENOMA											X		X				X					X				7
FIBROADENOCARCINOMA																										1
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*
ADENOCARCINOMA, NOS										X																1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																									X	1
LEIOMYOMA																										1
ENDOMETRIAL STROMAL POLYP		X				X		X									X	X				X	X			10
CARCINOSARCOMA																			X							1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR																						X				1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA	X																									1
SPECIAL SENSE ORGANS																										
ZYMBAL'S 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*
ADENOCARCINOMA, 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							X						X		X		11

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
SARCOMA, NOS				5 (10%)
FIBROMA	1 (2%)			
FIBROSARCOMA				1 (2%)
NEUROFIBROSARCOMA		1 (2%)	1 (2%)	2 (4%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	2 (4%)	2 (4%)	1 (2%)
FIBROSARCOMA			1 (2%)	
NEUROFIBROSARCOMA		2 (4%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(49)	(49)
CARCINOMA, NOS, METASTATIC		1 (2%)		
HEPATOCELLULAR CARCINOMA, METAST	4 (8%)	3 (6%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	4 (8%)	3 (6%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	1 (2%)	4 (8%)
PAPILLARY CYSTADENOCARCINOMA,MET			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	2 (4%)	2 (4%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	3 (6%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	1 (2%)	1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS			1 (2%)	
#SPLEEN	(48)	(49)	(49)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LYMPH NODE	(34)	(32)	(32)	(38)
SARCOMA, NOS, METASTATIC			1 (3%)	
#MESENTERIC L. NODE	(34)	(32)	(32)	(38)
CARCINOMA, NOS, METASTATIC		1 (3%)		
MALIGNANT LYMPHOMA, MIXED TYPE				1 (3%)
#AXILLARY LYMPH NODE	(34)	(32)	(32)	(38)
SARCOMA, NOS, METASTATIC			1 (3%)	
#PEYER'S PATCH	(43)	(45)	(40)	(42)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (3%)	
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
#BONE MARROW	(49)	(48)	(48)	(48)
HEMANGIOSARCOMA	1 (2%)		1 (2%)	1 (2%)
#SPLEEN	(48)	(49)	(49)	(47)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA	1 (2%)	1 (2%)		2 (4%)
#MYOCARDIUM	(50)	(50)	(49)	(49)
HEMANGIOMA		1 (2%)		
#LIVER	(50)	(50)	(49)	(48)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	2 (4%)	1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(49)	(48)
HEPATOCELLULAR ADENOMA	7 (14%)	5 (10%)	5 (10%)	5 (10%)
HEPATOCELLULAR CARCINOMA	14 (28%)	12 (24%)	13 (27%)	10 (21%)
LIPOSARCOMA	1 (2%)			
*GALLBLADDER	(50)	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(41)	(33)	(40)
ADENOMA, NOS		1 (2%)		
#ADRENAL	(46)	(50)	(47)	(47)
CORTICAL ADENOMA	1 (2%)	1 (2%)		1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	3 (6%)	
#ADRENAL/CAPSULE	(46)	(50)	(47)	(47)
ADENOMA, NOS				1 (2%)
#THYROID	(42)	(39)	(47)	(42)
PAPILLARY ADENOMA	1 (2%)			
FOLLICULAR-CELL ADENOMA	2 (5%)			1 (2%)
#THYROID FOLLICLE	(42)	(39)	(47)	(42)
PAPILLARY CYSTADENOMA, NOS			1 (2%)	
#PANCREATIC ISLETS	(47)	(49)	(47)	(48)
ISLET-CELL ADENOMA	1 (2%)			
REPRODUCTIVE SYSTEM				
NONE				
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(50)	(50)
OLIGODENDROGLIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)		
PAPILLARY ADENOMA	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PAPILLARY CYSTADENOMA, NOS	1 (2%)		1 (2%)	1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS			1 (2%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)			
SARCOMA, NOS, METASTATIC				1 (2%)
DIAPHRAGM				
CARCINOMA, NOS, INVASIVE		1		
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	13	8	12	15
MORIBUND SACRIFICE	3	3	8	5
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	34	39	28	29
DOSING ACCIDENT			2	1
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS				
ANIMAL MISSING				
ANIMAL MISSEXED				
OTHER CASES				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	30	30	31	35
TOTAL PRIMARY TUMORS	45	43	47	49
TOTAL ANIMALS WITH BENIGN TUMORS	18	12	13	13
TOTAL BENIGN TUMORS	21	16	14	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	19	23	27	27
TOTAL MALIGNANT TUMORS	24	27	33	34
TOTAL ANIMALS WITH SECONDARY TUMORS#	4	3	7	2
TOTAL SECONDARY TUMORS	4	6	8	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	3 (6%)	1 (2%)
RHABDOMYOSARCOMA		1 (2%)		
NEUROFIBROSARCOMA				2 (4%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	1 (2%)	1 (2%)	3 (6%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		1 (2%)	2 (4%)
PAPILLARY CYSTADENOCARCINOMA,MET	1 (2%)			
NEUROFIBROSARCOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	3 (6%)	1 (2%)	1 (2%)	
MALIG.LYMPHOMA, UNDIFFER-TYPE				1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	6 (12%)	2 (4%)	6 (12%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	4 (8%)	4 (8%)	1 (2%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)		1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		1 (2%)		
#SPLEEN	(47)	(50)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	1 (2%)		2 (4%)
#SPLENIC FOLLICLES	(47)	(50)	(49)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)			
#BRONCHIAL LYMPH NODE	(36)	(33)	(42)	(34)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#INGUINAL LYMPH NODE	(36)	(33)	(42)	(34)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (3%)		
#LIVER	(48)	(50)	(50)	(50)
KUPFFER-CELL SARCOMA			1 (2%)	
#GASTRIC SUBMUCOSA	(48)	(47)	(49)	(46)
MAST-CELL SARCOMA				1 (2%)
#THYMUS	(41)	(42)	(41)	(38)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		2 (5%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)		1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)	
#SPLEEN	(47)	(50)	(49)	(49)
HEMANGIOMA			1 (2%)	
HEMANGIOSARCOMA		1 (2%)		
#UTERUS	(48)	(50)	(50)	(48)
HEMANGIOSARCOMA		1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(50)	(50)	(48)
HEMANGIOMA	1 (2%)			
#OVARY	(40)	(47)	(43)	(45)
HEMANGIOMA		1 (2%)		1 (2%)
HEMANGIOSARCOMA			1 (2%)	
DIGESTIVE SYSTEM				
*TONGUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)		1 (2%)
#LIVER	(48)	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	4 (8%)	2 (4%)	2 (4%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	4 (8%)	1 (2%)	5 (10%)	1 (2%)
#ESOPHAGUS	(50)	(48)	(49)	(48)
SQUAMOUS CELL CARCINOMA	1 (2%)			
#GASTRIC MUCOSA	(48)	(47)	(49)	(46)
ADENOMATOUS POLYP, NOS	1 (2%)			
#ILEUM	(45)	(47)	(45)	(43)
SARCOMA, NOS, INVASIVE				1 (2%)
URINARY SYSTEM				
NONE				
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(39)	(38)	(38)
CARCINOMA,NOS				1 (3%)
ADENOMA, NOS	5 (12%)	4 (10%)	1 (3%)	3 (8%)
#ADRENAL/CAPSULE	(49)	(49)	(50)	(49)
ADENOMA, NOS		1 (2%)		
#ZONA FASCICULATA	(49)	(49)	(50)	(49)
ADENOMA, NOS			1 (2%)	
#THYROID	(40)	(42)	(43)	(44)
PAPILLARY ADENOMA		1 (2%)		
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(44)	(47)	(50)	(47)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)	1 (2%)
#UTERUS	(48)	(50)	(50)	(48)
LEIOMYOMA	1 (2%)			
LEIOMYOSARCOMA	2 (4%)		3 (6%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOMETRIAL STROMAL POLYP	1 (2%)	3 (6%)	1 (2%)	2 (4%)
#UTERUS/ENDOMETRIUM	(48)	(50)	(50)	(48)
CARCINOMA,NOS			1 (2%)	
#ENDOMETRIAL GLAND	(48)	(50)	(50)	(48)
ADENOCARCINOMA, NOS				1 (2%)
#OVARY	(40)	(47)	(43)	(45)
SARCOMA, NOS, INVASIVE		1 (2%)		
TERATOMA, NOS			1 (2%)	
NERVOUS SYSTEM				
#BRAIN	(50)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE				1 (2%)
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
PAPILLARY CYSTADENOMA, NOS				1 (2%)
PAPILLARY CYSTADENOCARCINOMA,NOS	1 (2%)			
MUSCULOSKELETAL SYSTEM				
*LUMBAR VERTEBRA	(50)	(50)	(50)	(50)
OSTEOSARCOMA				1 (2%)
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)			
*PERITONEUM	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)	
*PLEURA	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (2%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
SARCOMA, NOS, METASTATIC				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	8	7	6	9
MORIBUND SACRIFICE	5	3	3	3
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	37	40	41	37
DOSING ACCIDENT				1
ACCIDENTALLY KILLED, NDA				
ACCIDENTALLY KILLED, NOS				
ANIMAL MISSING				
ANIMAL MISSEXED				
OTHER CASES				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	25	26	29
TOTAL PRIMARY TUMORS	43	36	38	38
TOTAL ANIMALS WITH BENIGN TUMORS	15	11	8	11
TOTAL BENIGN TUMORS	17	15	8	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	18	22	23
TOTAL MALIGNANT TUMORS	26	21	28	25
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	1	3
TOTAL SECONDARY TUMORS	3	2	1	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2	
TOTAL UNCERTAIN TUMORS			2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	104	105	103	104	104	104	105	088	105	105	105	105	092	101	105	105	102	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
FIBROMA																									
SUBCUTANEOUS TISSUE	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
SARCOMA, NOS																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																X	X								
ALVEOLAR/BRONCHIOLAR ADENOMA		X																							X
ALVEOLAR/BRONCHIOLAR CARCINOMA		X																							
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
SPLEEN	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
HEMANGIOSARCOMA	X																								
LYMPH NODES	+	+	+	+	+	-	+	-	-	+	+	-	+	+	+	-	-	+	+	+	+	-	-	+	+
THYMUS	-	+	+	+	-	-	-	-	-	-	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X				X			X		X													X	X
HEPATOCELLULAR CARCINOMA																X	X								
LIPOSARCOMA																									
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	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	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	-	-	+	A	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+
CORTICAL ADENOMA														X											
PHEOCHROMOCYTOMA						X																			
THYROID	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+
PAPILLARY ADENOMA																									
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	-	-	-	-	-	-	+	-	+	-	-	+	+	-	+	+	A	-	-	+	+	-	-
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	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	A	+	-	-	+	+	+
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
PAPILLARY ADENOMA														X											
PAPILLARY CYSTADENOMA, 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
SARCOMA, NOS					X																				
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE	X																							X	

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) UNTREATED CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	012	098	104	097	105	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	50M
FIBROMA																	X									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	50M
SARCOMA, NOS				X																						1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA				X					X																	4
ALVEOLAR/BRONCHIOLAR ADENOMA															X						X				X	5
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																X										1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										1
LYMPH NODES	+	-	-	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	-	34
THYMUS	+	-	-	-	+	+	+	+	+	+	+	+	+	+	-	-	+	-	-	+	+	+	+	+	-	32
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA				X			X	X		X							X									7
HEPATOCELLULAR CARCINOMA				X				X	X					X		X		X			X			X		14
LIPOSARCOMA																X										1
HEMANGIOSARCOMA					X																					1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	+	N	+	N	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	39
ADRENAL	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA																										1
THYROID	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	42
PAPILLARY ADENOMA							X																			1
FOLLICULAR-CELL ADENOMA												X									X					2
PARATHYROID	-	-	-	+	+	+	+	-	+	+	+	-	-	+	+	+	-	+	+	-	-	+	-	-	+	24
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA																										1
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	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
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	50M
PAPILLARY ADENOMA																			X							1
PAPILLARY CYSTADENOMA, NOS																										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	50M
SARCOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																	X									1
MALIGNANT LYMPHOMA, MIXED TYPE																										2

M: ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	086	091	105	105	091	105	105	105	105	105	058	105	105	105
INTEGUMENTARY SYSTEM																									
SKIN	N	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																X									
NEUROFIBROSARCOMA																									
SUBCUTANEOUS TISSUE	N	N	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	N	+	+	+	+	+	+	+
SARCOMA, NOS																						X			
NEUROFIBROSARCOMA																	X								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC													X												
HEPATOCELLULAR CARCINOMA, METASTA		X									X														X
ALVEOLAR/BRONCHIOLAR ADENOMA													X			X									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	-	-	+	+	+	-	-	+	+	+	-	+	-	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	-	-	+	+	+	-	-	-	-	+	+	-	+	+	+	+	+	-	+	-	+	-	+	-	-
CARCINOMA, NOS, METASTATIC																									
THYMUS	+	-	+	+	+	-	+	+	+	+	-	-	+	-	+	+	-	-	+	+	-	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																			X						
HEPATOCELLULAR CARCINOMA	X		X								X		X					X					X		
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	+	N	N	+	N	+	+
CARCINOMA,NOS																									
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	-	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	+	+	+
ADENOMA, NOS												X													
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA		X																							
PHEOCHROMOCYTOMA											X														
THYROID	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+
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																									
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									
DIAPHRAGM NOS																									
CARCINOMA, NOS, INVASIVE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	094	105	105	105	105	105	088	103	105	097	105	105	105	105	105	095	075	105	105	079	105	098	105	105	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																										1
NEUROFIBROSARCOMA																	X									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS		X																					X			2
NEUROFIBROSARCOMA																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, METASTATIC																					X					1
HEPATOCELLULAR CARCINOMA, METASTA																					X		X			3
ALVEOLAR/BRONCHIOLAR ADENOMA																	X									4
ALVEOLAR/BRONCHIOLAR CARCINOMA																										2
TRACHEA	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	41
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	48
SPLEEN	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																							X			1
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	-	+	+	+	-	+	+	+	+	-	32
CARCINOMA, NOS, METASTATIC																					X					1
THYMUS	+	-	+	+	-	+	+	-	+	+	-	+	+	+	+	+	-	-	+	+	-	-	+	+	+	33
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																							X			1
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X									X					X								X			5
HEPATOCELLULAR CARCINOMA			X						X				X		X						X		X			12
HEMANGIOSARCOMA																									X	1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	50M
CARCINOMA,NOS																					X					1
PANCREAS	+	-	+	+	+	+	+	+	+	+	•	•	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	45
LARGE INTESTINE	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+	+	+	+	41
ADENOMA, NOS																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																	X									1
PHEOCHROMOCYTOMA																										2
THYROID	-	-	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	39
PARATHYROID	-	-	+	-	-	-	-	-	+	+	-	+	-	-	+	+	+	+	+	-	+	+	-	+	+	22
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	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50M
ADENOMA, 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	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X			X				2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X										X								2
MALIGNANT LYMPHOMA, MIXED TYPE											X															1
DIAPHRAGM NOS																										
CARCINOMA, NOS, INVASIVE																					X					1

M ANIMALS NECROPSIED
+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	087	090	051	094	094	055	051	048	030	032	032	044	076	051	037	045	055	098	044	055	051	052	055	055	051
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+
NEUROFIBROSARCOMA														X											
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																	X			X					
ALVEOLAR/BRONCHIOLAR ADENOMA																								X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
PAPILLARY CYSTADENOCARCINOMA,META																									
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
HEMANGIOSARCOMA										X															
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
HEMANGIOMA																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LYMPH NODES	+	-	+	+	-	+	-	+	-	+	+	-	-	-	+	+	+	-	+	+	+	+	-	-	+
SARCOMA, NOS, METASTATIC																									
THYMUS	-	+	+	-	-	+	+	+	+	-	-	-	-	-	+	-	+	-	-	-	-	+	+	+	
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																	X								
HEPATOCELLULAR CARCINOMA										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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
SMALL INTESTINE	-	+	+	+	-	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	-	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																								X	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	-	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	-	+	-	-	+	+	-	-	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
PHEOCHROMOCYTOMA														X											
THYROID	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OLIGODENDROGLIOMA																									
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
PAPILLARY CYSTADENOMA, NOS																	X								
PAPILLARY CYSTADENOCARCINOMA,NOS																									
BODY CAVITIES																									
PERITONEUM	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, NOS																	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
HEMANGIOSARCOMA, 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
HEMANGIOSARCOMA															X										
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																					X				
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																X			X						
MALIGNANT LYMPHOMA, MIXED TYPE																				X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	082	105	105	101	095	105	105	105	086	105	105	105	105	101	105	052	105	105	089	032	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
NEUROFIBROSARCOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS			X																			X				2
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA					X															X						4
ALVEOLAR/BRONCHIOLAR ADENOMA												X												X		3
ALVEOLAR/BRONCHIOLAR CARCINOMA																									X	1
PAPILLARY CYSTADENOCARCINOMA,META							X																			1
TRACHEA	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
HEMANGIOSARCOMA																										1
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA																						X				1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								X		1
LYMPH NODES	+	-	+	-	-	+	+	+	-	+	+	+	+	-	-	+	-	+	-	+	+	+	+	+	+	32
SARCOMA, NOS, METASTATIC																						Xa				1
THYMUS	+	-	+	-	-	+	-	+	-	-	+	+	+	+	+	-	+	+	-	-	+	-	+	-	+	25
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA						X	X					X			X											5
HEPATOCELLULAR CARCINOMA		X		X	X			X				X			X				X							13
HEMANGIOSARCOMA										X																2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
STOMACH	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	46
SMALL INTESTINE	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	40
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LARGE INTESTINE	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	41
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	42
ENDOCRINE SYSTEM																										
PITUITARY	+	-	-	-	-	+	-	+	+	+	+	-	-	+	+	+	-	+	-	+	+	+	+	+	+	33
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
PHEOCHROMOCYTOMA				X															X							3
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PAPILLARY CYSTADENOMA, NOS								X																		1
PARATHYROID	-	+	-	+	+	-	+	+	-	-	-	-	-	-	-	+	-	+	-	+	+	-	+	+	+	25
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	50M
TESTIS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OLIGODENDROGLIOMA	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	50M
PAPILLARY CYSTADENOMA, NOS																										1
PAPILLARY CYSTADENOCARCINOMA,NOS							X																			1
BODY CAVITIES																										
PERITONEUM	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	50M
MALIGNANT LYMPHOMA, NOS																										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	50M
HEMANGIOSARCOMA, 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	50M
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																						X				2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE					X																					3
MALIGNANT LYMPHOMA, MIXED TYPE																										1

M ANIMALS NECROPSIED
a: MULTIPLE OCCURENCE OF MORPHOLOGY
+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
MI: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	095	072	151	093	105	089	071	105	105	085	115	105	105	105	100	105	105	105	105	105	115	087	115	105	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS	X			X	X		X																		
FIBROSARCOMA																				X					
NEUROFIBROSARCOMA																								X	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS										X															
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																						X			
ALVEOLAR/BRONCHIOLAR ADENOMA																						X			
ALVEOLAR/BRONCHIOLAR CARCINOMA								X			X						X							X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	-	-	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE																							X		
THYMUS	-	-	-	-	-	+	-	+	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X						X													
HEPATOCELLULAR CARCINOMA								X	X						X			X		X		X	X	
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	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							
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
PAPILLARY CYSTADENOMA, 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
SARCOMA, NOS, METASTATIC																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50M
SARCOMA, NOS	5
FIBROSARCOMA	1
NEUROFIBROSARCOMA	2
SUBCUTANEOUS TISSUE	50M
SARCOMA, NOS	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	49
HEPATOCELLULAR CARCINOMA, METASTA	1
ALVEOLAR/BRONCHIOLAR ADENOMA	6
ALVEOLAR/BRONCHIOLAR CARCINOMA	4
TRACHEA	48
HEMATOPOIETIC SYSTEM	
BONE MARROW	48
HEMANGIOSARCOMA	1
SPLEEN	47
HEMANGIOSARCOMA	2
LYMPH NODES	38
MALIGNANT LYMPHOMA, MIXED TYPE	1
THYMUS	31
CIRCULATORY SYSTEM	
HEART	49
DIGESTIVE SYSTEM	
SALIVARY GLAND	48
LIVER	48
HEPATOCELLULAR ADENOMA	5
HEPATOCELLULAR CARCINOMA	10
HEMANGIOSARCOMA	1
BILE DUCT	48
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	48
ESOPHAGUS	49
STOMACH	46
SMALL INTESTINE	42
LARGE INTESTINE	47
URINARY SYSTEM	
KIDNEY	48
URINARY BLADDER	47
ENDOCRINE SYSTEM	
PITUITARY	40
ADRENAL	47
ADENOMA, NOS	1
CORTICAL ADENOMA	1
THYROID	42
FOLLICULAR-CELL ADENOMA	1
PARATHYROID	22
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
TESTIS	49
PROSTATE	48
NERVOUS SYSTEM	
BRAIN	50
SPECIAL SENSE ORGANS	
HARDERIAN GLAND	50M
PAPILLARY CYSTADENOMA, NOS	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
SARCOMA, NOS, METASTATIC	1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	115	105	105	105	105	105	096	105	105	105	105	105	105	105	105	105	105	105	092	105	105	105	105	078
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA	X																								
ALVEOLAR/BRONCHIOLAR CARCINOMA																						X			
PAPILLARY CYSTADENOCARCINOMA,META													X												
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE									X		X														
LYMPH NODES	+	-	+	+	+	-	+	-	-	-	+	+	-	-	+	-	+	+	+	-	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA							X																		
HEPATOCELLULAR CARCINOMA				X											X				X		X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	N	N	+	+	N	N	N	+	+	N	N	N	+	+	+	+	+	N	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS																			X						
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+
ADENOMA, NOS																						X		X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	-	+	+	+
PARATHYROID	-	+	-	-	-	-	-	+	+	+	-	+	+	-	+	+	-	+	-	+	-	-	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	+	N	+	+	N	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOMA																									
LEIOMYOSARCOMA																									X
ENDOMETRIAL STROMAL POLYP																					X				
HEMANGIOMA																									
OVARY	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
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
PAPILLARY CYSTADENOCARCINOMA,NOS													X												
BODY CAVITIES																									
PLEURA	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
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																						X			
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
ALVEOLAR/BRONCHIOLAR CA, METASTAT																						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, NOS																						X			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				X		X										X	X								
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X																	
MALIGNANT LYMPHOMA, MIXED TYPE																							X		

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) UNTREATED CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	103	105	100	076	105	105	105	105	084	085	051	105	105	105	095	105	105	091	081	080	081	081	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA			X							X																3
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
PAPILLARY CYSTADENOCARCINOMA,META																										1
TRACHEA	+	+	-	A	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										2
LYMPH NODES	+	+	+	A	+	+	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	36
THYMUS	+	-	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR ADENOMA		X														X		X								4
HEPATOCELLULAR CARCINOMA																										4
BILE DUCT	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	+	+	N	+	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	50M
PANCREAS	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA																	X									1
STOMACH	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMATOUS POLYP, NOS																										1
SMALL INTESTINE	+	+	+	A	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	45
LARGE INTESTINE	+	+	+	A	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	-	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY BLADDER	+	+	+	A	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+	41
ADENOMA, NOS						X							X						X							5
ADRENAL	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	-	+	-	A	+	-	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	40
PARATHYROID	-	-	-	A	+	-	+	-	+	+	-	-	-	-	+	+	-	-	+	-	+	+	-	-	+	22
PANCREATIC ISLETS	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	44
ISLET-CELL ADENOMA										X																1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	N	+	+	N	+	+	N	N	+	+	+	N	N	+	+	+	N	N	+	N	50M
UTERUS	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LEIOMYOMA																			X							1
LEIOMYOSARCOMA																			X							2
ENDOMETRIAL STROMAL POLYP																										1
HEMANGIOMA									X																	1
OVARY	+	+	-	A	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	40
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	50M
PAPILLARY CYSTADENOCARCINOMA,NOS																										1
BODY CAVITIES																										
PLEURA	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	50M
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										1
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	50M
ALVEOLAR/BRONCHIOLAR CA, METASTAT																										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	50M
MALIGNANT LYMPHOMA, NOS						X												X								3
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE							X		X																	6
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X								X		X			4
MALIGNANT LYMPHOMA, MIXED TYPE	X																									2

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

!: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	101	105	105	105	105	105	105	105	105	105	069	051	101	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS									X																
RHABDOMYOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC																			X						
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	-	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																				X					
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												X													
LYMPH NODES	-	+	+	+	+	+	+	-	-	+	-	+	-	-	-	+	+	+	+	+	+	+	+	+	-
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
THYMUS	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X						X																
MALIGNANT LYMPHOMA, MIXED TYPE		X																							
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 CARCINOMA									X																
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA															X										
HEPATOCELLULAR CARCINOMA															X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
PANCREAS	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-
ADENOMA, NOS										X				X											
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																	X								
THYROID	+	+	+	+	+	+	-	+	-	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	+
PAPILLARY ADENOMA														X											
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	-	-	-	+	-	-	-	+	-	+	-	-	-	-	-	-	+	-	-	+	+	-	-
PANCREATIC ISLETS	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	N	+	N	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	N
ADENOCARCINOMA, NOS																			X						
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																X									
HEMANGIOSARCOMA																									
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS, INVASIVE					X																				
HEMANGIOMA																									
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, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE														X											
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		X														X									
LYMPHOCYTIC LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	096	105	011	105	105	105	105	104	093	105	105	105	103	105	105	103	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS														X												1
RHABDOMYOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC																					X					1
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LYMPH NODES	-	+	+	+	-	-	-	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	-	-	33
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												X														1
THYMUS	+	+	+	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	42
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										2
MALIGNANT LYMPHOMA, MIXED TYPE																										1
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	50M
SQUAMOUS CELL CARCINOMA																										1
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																					+					2
HEPATOCELLULAR CARCINOMA																					X					1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	-	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	39
ADENOMA, NOS			X																					X		4
ADRENAL	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS																										1
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	42
PAPILLARY ADENOMA																										1
FOLLICULAR-CELL ADENOMA										X																1
PARATHYROID	+	-	-	+	-	+	+	+	+	+	-	-	-	+	+	-	-	-	-	-	-	+	+	+	+	21
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA						X																				1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	50M
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP										X											X	X				3
HEMANGIOSARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	47
SARCOMA, NOS, INVASIVE														X												1
HEMANGIOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50M
HEMANGIOSARCOMA				X																						1
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X							2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	X					X																				4
LYMPHOCYTIC LEUKEMIA												X														1

M ANIMALS NECROPSIED
+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

LOW DOSE

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	0 9 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 6	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 3	1 0 5	1 0 7	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
HEMANGIOSARCOMA																			X						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA		X																							
ALVEOLAR/BRONCHIOLAR CARCINOMA	X																								
TRACHEA	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X						
LYMPH NODES	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
THYMUS	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	-	+	+	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA														X					X						
KUPFFER-CELL SARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	N	N	+	+	+	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS								X																	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	+	+	-	+	+	-	-	-	-	+	-	+	+	+	-	+	+	+	+	+	+	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	N	+	N	+	+	N	N	+	+	+	+	N	+	+	N	+	+	+
ADENOCARCINOMA, NOS						X																			
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
LEIOMYOSARCOMA		X				X								X											
ENDOMETRIAL STROMAL POLYP																									
OVARY	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	-	-	+	
TERATOMA, NOS																				X					
HEMANGIOSARCOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
PERITONEUM	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
MESOTHELIOMA, NOS								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
LEIOMYOSARCOMA, INVASIVE														X											
MALIGNANT LYMPHOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X							X										
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0226	0227	0228	0229	0230	0231	0232	0233	0234	0235	0236	0237	0238	0239	0240	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL
WEEKS ON STUDY	0931	1005	1005	0850	1005	1005	1005	1101	1005	0851	1005	1005	1005	1005	0904	1005	1005	1005	1005	0903	1005	1005	1005	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS	X							X												X						3
HEMANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA																				X						1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LYMPH NODES	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	42
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE												X														1
THYMUS	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	41
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X																							X	2
HEPATOCELLULAR CARCINOMA															X					X	X					5
KUPFFER-CELL SARCOMA																	X									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	N	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	+	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
STOMACH	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	45
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	-	-	+	-	+	+	-	-	+	+	+	+	+	+	-	+	+	-	-	38
ADENOMA, NOS											X															1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																										1
THYROID	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	43
FOLLICULAR-CELL ADENOMA																	X									1
PARATHYROID	+	-	+	-	-	-	-	+	-	+	+	-	+	-	+	-	-	-	-	-	-	-	+	+	-	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	N	+	+	N	N	+	+	+	+	N	+	N	+	+	+	N	N	+	+	N	+	+	50M
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	a	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS																										1
LEIOMYOSARCOMA			X																							3
ENDOMETRIAL STROMAL POLYP								X																		1
OVARY	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	43
TERATOMA, NOS				X																						1
HEMANGIOSARCOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
PERITONEUM	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	50M
MESOTHELIOMA, NOS																										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	50M
LEIOMYOSARCOMA, INVASIVE																										1
MALIGNANT LYMPHOMA, NOS															X											1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	X						X				X													X		6
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X												1
MALIGNANT LYMPHOMA, MIXED TYPE																								X		1

a ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR STUDY OF CHLOROBENZENE

HIGH DOSE

ANIMAL NUMBER	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 1 6	0 0 1 7	0 0 1 8	0 0 1 9	0 0 2 0	0 1 1 1	0 1 1 2	0 1 1 3	0 1 1 4	0 1 1 5	0 1 1 6	0 1 1 7	0 1 1 8	0 1 1 9	0 2 2 0	0 2 2 1	0 2 2 2	0 2 2 3	0 2 2 4	0 2 2 5
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 4	1 0 5	1 0 5	1 0 3	0 9 3	1 0 5	1 0 5	1 0 5	1 0 5	0 7 2	1 0 3	0 8 1	1 0 5
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
NEUROFIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	X	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA														X											
NEUROFIBROSARCOMA, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE															X					X					
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
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	X	N	N
SQUAMOUS CELL CARCINOMA																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X																						
HEPATOCELLULAR CARCINOMA									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+
MAST-CELL SARCOMA													X												
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+
SARCOMA, NOS, INVASIVE																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+
CARCINOMA,NOS			X																					X	
ADENOMA, NOS																		X							
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	-	-	-	+	+	-	-	+	-	-	-	+	-	+	-	+	+	+	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+
ISLET-CELL ADENOMA																								X	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	N	+	N	+	+	+	+	+	+	+	N	+	N	+	N	+	+	N	+	N	+	N	+
ADENOCARCINOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
ADENOCARCINOMA, NOS														X											
ENDOMETRIAL STROMAL POLYP												X													
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
HEMANGIOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, INVASIVE																								X	
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
PAPILLARY CYSTADENOMA, NOS						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																									
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, METASTATIC																									
HEMANGIOSARCOMA																									
MALIG.LYMPHOMA, UNDIFFER-TYPE					X			X	X						X								X		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																	X								
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X			
MALIGNANT LYMPHOMA, MIXED TYPE	X																								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	02616	02627	02628	02629	03301	03311	03312	03314	03315	03316	03317	03318	03319	04401	04411	04412	04413	04414	04415	04416	04417	04418	04419	05001	TOTAL
WEEKS ON STUDY	10351	10351	10351	10353	10355	10414	10355	10355	10355	10355	10355	10355	10355	10357	10355	10355	10355	10355	10355	10355	10355	10355	10355	10355	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	+	+	+	+	+	50M
SARCOMA, NOS												X													1
NEUROFIBROSARCOMA	X					X																			2
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																		X							3
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																		2
NEUROFIBROSARCOMA, METASTATIC						X																			1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE								X																	2
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												X													2
LYMPH NODES	-	+	+	+	+	+	+	-	+	+	-	+	+	+	-	-	+	+	+	+	-	+	+	-	34
THYMUS	+	-	-	+	+	-	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	38
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	50M
SQUAMOUS CELL CARCINOMA																									1
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																									1
HEPATOCELLULAR CARCINOMA																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	N	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	46
MAST-CELL SARCOMA																									1
SMALL INTESTINE	+	+	+	-	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	43
SARCOMA, NOS, INVASIVE												X													1
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	-	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	-	+	-	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	38
CARCINOMA,NOS																									1
ADENOMA, NOS																							X		3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	44
FOLLICULAR-CELL ADENOMA								X																	1
PARATHYROID	+	+	-	-	+	+	-	+	+	+	+	-	-	-	+	-	+	-	-	-	+	+	-	+	23
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA																									1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	N	+	+	N	+	+	+	+	N	N	+	N	N	+	N	+	+	+	+	+	N	+	50M
ADENOCARCINOMA, NOS									X																1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS																									1
ENDOMETRIAL STROMAL POLYP																							X		2
OVARY	+	-	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	45
HEMANGIOMA																							X		1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, INVASIVE																									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	50M
PAPILLARY CYSTADENOMA, NOS																									1
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	50M
OSTEOSARCOMA																		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	50M
SARCOMA, NOS, METASTATIC												X													1
HEMANGIOSARCOMA																							X		1
MALIG.LYMPHOMA, UNDIFFER-TYPE														X											1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									2
MALIGNANT LYMPHOMA, MIXED TYPE																									1

M ANIMALS NECROPSIED
A: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS		1 (2%)		
RESPIRATORY SYSTEM				
#TRACHEA	(50)	(50)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
#LUNG/BRONCHIOLE	(50)	(50)	(50)	(50)
ECTOPIA			1 (2%)	
CYST, NOS	1 (2%)			
#LUNG	(50)	(50)	(50)	(50)
ASPIRATION, FOREIGN BODY		4 (8%)	15 (30%)	10 (20%)
CONGESTION, NOS			1 (2%)	
EDEMA, NOS	1 (2%)	1 (2%)		
HEMORRHAGE	1 (2%)	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		2 (4%)	
PNEUMONIA, ASPIRATION		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	7 (14%)	2 (4%)	9 (18%)	4 (8%)
INFLAMMATION, FOCAL GRANULOMATOU		11 (22%)	4 (8%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	2 (4%)	3 (6%)	
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(49)	(47)	(47)
MYELOFIBROSIS		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, GRANULOCYTIC	6 (13%)	2 (4%)	3 (6%)	
HYPERPLASIA, RETICULUM CELL	1 (2%)	2 (4%)	1 (2%)	
HYPOPLASIA, HEMATOPOIETIC		2 (4%)		
HYPOPLASIA, ERYTHROID	1 (2%)			
#SPLEEN	(48)	(50)	(49)	(47)
FIBROSIS, FOCAL				1 (2%)
NECROSIS, FOCAL	1 (2%)			
LYMPHOID DEPLETION	1 (2%)	3 (6%)		3 (6%)
#SPLENIC CAPSULE	(48)	(50)	(49)	(47)
HYPERPLASIA, MESOTHELIAL		1 (2%)		
#SPLENIC RED PULP	(48)	(50)	(49)	(47)
CONGESTION, NOS	1 (2%)			
PIGMENTATION, NOS	1 (2%)	1 (2%)	1 (2%)	
HEMATOPOIESIS	1 (2%)			1 (2%)
#MANDIBULAR L. NODE	(43)	(38)	(43)	(37)
CYST, NOS	1 (2%)		4 (9%)	
CONGESTION, NOS	11 (26%)	2 (5%)		3 (8%)
INFLAMMATION, ACUTE/CHRONIC		1 (3%)		
INFLAMMATION, FOCAL GRANULOMATOU		1 (3%)		
LYMPHOID DEPLETION			1 (2%)	
ANGIECTASIS			1 (2%)	
PLASMACYTOSIS	2 (5%)	3 (8%)		2 (5%)
ERYTHROPHAGOCYTOSIS	1 (2%)			
HYPERPLASIA, LYMPHOID				1 (3%)
HEMATOPOIESIS	1 (2%)			
#LYMPH NODE OF THORAX	(43)	(38)	(43)	(37)
CONGESTION, NOS	1 (2%)			
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			1 (3%)
PIGMENTATION, NOS			2 (5%)	
PLASMACYTOSIS			1 (2%)	
#MESENTERIC L. NODE	(43)	(38)	(43)	(37)
CONGESTION, NOS			1 (2%)	
INFLAMMATION, MULTIFOCAL	2 (5%)			2 (5%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION, FOCAL GRANULOMATOU		1 (3%)	1 (2%)	
LYMPHOID DEPLETION		1 (3%)		
#GASTRIC FUNDUS	(48)	(50)	(49)	(48)
HYPERPLASIA, LYMPHOID				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#COLON	(48)	(48)	(48)	(47)
HYPERPLASIA, LYMPHOID				1 (2%)
#THYMUS	(42)	(45)	(43)	(41)
EMBRYONAL DUCT CYST	1 (2%)			
HEMORRHAGE				1 (2%)
#THYMIC MEDULLA	(42)	(45)	(43)	(41)
HEMORRHAGE				1 (2%)
CIRCULATORY SYSTEM				
#MANDIBULAR L. NODE	(43)	(38)	(43)	(37)
LYMPHANGIECTASIS	1 (2%)			
#LUNG	(50)	(50)	(50)	(50)
PERIVASCULITIS	1 (2%)			2 (4%)
#HEART/ATRIUM	(50)	(50)	(50)	(50)
THROMBOSIS, NOS	2 (4%)			
#LEFT ATRIUM	(50)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)			
#MYOCARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
DEGENERATION, NOS	48 (96%)	41 (82%)	45 (90%)	36 (72%)
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
*CAROTID ARTERY	(50)	(50)	(50)	(50)
PERIARTERITIS			1 (2%)	
*PULMONARY VEIN	(50)	(50)	(50)	(50)
THROMBUS, MURAL		1 (2%)		
#HEPATIC SINUSOID	(50)	(50)	(49)	(49)
CONGESTION, NOS			2 (4%)	
#PANCREAS	(48)	(50)	(48)	(48)
PERIARTERITIS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
*UPPER LIP	(50)	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
#SALIVARY GLAND	(49)	(50)	(49)	(45)
DILATATION/DUCTS		2 (4%)		
ATROPHY, FOCAL	1 (2%)	1 (2%)		
#LIVER	(50)	(50)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION, FOCAL GRANULOMATOU	9 (18%)	9 (18%)	3 (6%)	
ADHESION, FIBROUS		1 (2%)		
DEGENERATION, NOS				1 (2%)
DEGENERATION, CYSTIC	5 (10%)	2 (4%)	5 (10%)	
LIPOIDOSIS		1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)		4 (8%)
BASOPHILIC CYTO CHANGE	25 (50%)	27 (54%)	6 (12%)	3 (6%)
EOSINOPHILIC CYTO CHANGE	4 (8%)	1 (2%)	2 (4%)	2 (4%)
CLEAR-CELL CHANGE	2 (4%)	5 (10%)		1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)	(49)
CONGESTION, NOS			1 (2%)	
DEGENERATION, NOS	2 (4%)			2 (4%)
NECROSIS, NOS	1 (2%)	1 (2%)		1 (2%)
NECROSIS, FOCAL	1 (2%)		4 (8%)	4 (8%)
CYTOPLASMIC VACUOLIZATION				1 (2%)
#LIVER/PERIPORTAL	(50)	(50)	(49)	(49)
METAMORPHOSIS FATTY				1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(49)	(49)
DEGENERATION, NOS	1 (2%)			
#BILE DUCT	(50)	(50)	(49)	(49)
HYPERPLASIA, NOS	2 (4%)			
HYPERPLASIA, FOCAL	47 (94%)	49 (98%)	43 (88%)	32 (65%)
#PANCREAS	(48)	(50)	(48)	(48)
DILATATION/DUCTS		1 (2%)		1 (2%)
NECROSIS, FAT	1 (2%)			
HYPERPLASIA, MESOTHELIAL			1 (2%)	
#PANCREATIC DUCT	(48)	(50)	(48)	(48)
HYPERTROPHY, NOS	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PANCREATIC ACINUS	(48)	(50)	(48)	(48)
ATROPHY, FOCAL	20 (42%)	10 (20%)	8 (17%)	9 (19%)
ATROPHY, DIFFUSE		1 (2%)		
#ESOPHAGUS	(50)	(50)	(49)	(50)
PENETRATING WOUND				1 (2%)
DILATATION, NOS			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#ESOPHAGEAL MUCOUS ME	(50)	(50)	(49)	(50)
HERNIA, NOS		1 (2%)		
#PERIESOPHAGEAL TISSU	(50)	(50)	(49)	(50)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)		
#STOMACH	(48)	(50)	(49)	(48)
ADHESION, NOS			1 (2%)	
HYPERKERATOSIS		1 (2%)		
#GASTRIC MUCOSA	(48)	(50)	(49)	(48)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#GASTRIC CARDIAC GLAN	(48)	(50)	(49)	(48)
ULCER, FOCAL				1 (2%)
ULCER, CHRONIC				1 (2%)
DYSPLASIA, NOS				1 (2%)
#GASTRIC SUBMUCOSA	(48)	(50)	(49)	(48)
EDEMA, NOS	1 (2%)			
#CARDIAC STOMACH	(48)	(50)	(49)	(48)
EPIDERMAL INCLUSION CYST		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
ULCER, CHRONIC			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERKERATOSIS			1 (2%)	
ACANTHOSIS			1 (2%)	
DYSPLASIA, NOS				1 (2%)
#GASTRIC FUNDUS	(48)	(50)	(49)	(48)
ULCER, FOCAL		1 (2%)		
#DUODENAL MUCOSA	(46)	(50)	(47)	(46)
HYPERPLASIA, FOCAL		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#DUODENAL SUBMUCOSA	(46)	(50)	(47)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#JEJUNUM	(46)	(50)	(47)	(46)
EMBRYONAL REST				1 (2%)
#COLON	(48)	(48)	(48)	(47)
NEMATODIASIS		2 (4%)		
PARASITISM	2 (4%)		2 (4%)	2 (4%)
#COLONIC SUBMUCOSA	(48)	(48)	(48)	(47)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(49)	(50)
MINERALIZATION		1 (2%)		
HYDRONEPHROSIS				1 (2%)
CONGESTION, PASSIVE			1 (2%)	
NEPHROPATHY	46 (92%)	42 (84%)	44 (90%)	43 (86%)
#KIDNEY/CORTEX	(50)	(50)	(49)	(50)
MINERALIZATION		1 (2%)		
CYST, NOS			1 (2%)	3 (6%)
MULTIPLE CYSTS			1 (2%)	1 (2%)
NEPHROPATHY			2 (4%)	
#KIDNEY/TUBULE	(50)	(50)	(49)	(50)
ECTOPIA	1 (2%)			
MINERALIZATION				1 (2%)
PIGMENTATION, NOS	2 (4%)			3 (6%)
#KIDNEY/PELVIS	(50)	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)	
#URINARY BLADDER	(48)	(48)	(46)	(45)
INFLAMMATION ACTIVE CHRONIC	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(50)	(42)	(47)
EMBRYONAL DUCT CYST		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE	1 (2%)			
HYPERPLASIA, FOCAL	6 (12%)	1 (2%)	3 (7%)	4 (9%)
#ANTERIOR PITUITARY	(49)	(50)	(42)	(47)
EMBRYONAL DUCT CYST		1 (2%)		2 (4%)
CYST, NOS				1 (2%)
MULTIPLE CYSTS				1 (2%)
CONGESTION, NOS			1 (2%)	
HEMORRHAGE		1 (2%)		
HYPERTROPHY, FOCAL		1 (2%)	2 (5%)	
#PITUITARY CELL	(49)	(50)	(42)	(47)
HYPERTROPHY, FOCAL				1 (2%)
#ADRENAL CORTEX	(49)	(49)	(49)	(49)
CONGESTION, NOS	1 (2%)			
DEGENERATION, NOS				1 (2%)
LIPOIDOSIS	1 (2%)	2 (4%)	4 (8%)	2 (4%)
#ZONA FASCICULATA	(49)	(49)	(49)	(49)
NECROSIS, FOCAL			1 (2%)	
LIPOIDOSIS	2 (4%)			
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(49)	(49)	(49)	(49)
CYST, NOS				1 (2%)
HYPERPLASIA, FOCAL	6 (12%)	3 (6%)	4 (8%)	3 (6%)
#THYROID	(49)	(50)	(49)	(43)
EMBRYONAL DUCT CYST			1 (2%)	1 (2%)
FOLLICULAR CYST, NOS	1 (2%)	1 (2%)	6 (12%)	
HYPERPLASIA, C-CELL	21 (43%)	21 (42%)	20 (41%)	22 (51%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)		
#THYROID FOLLICLE	(49)	(50)	(49)	(43)
HYPERPLASIA, CYSTIC		1 (2%)		
#PARATHYROID	(41)	(39)	(41)	(40)
HYPERPLASIA, NOS	2 (5%)	1 (3%)	1 (2%)	
HYPERPLASIA, FOCAL	3 (7%)		1 (2%)	
#PANCREATIC ISLETS	(48)	(50)	(48)	(48)
HYPERPLASIA, FOCAL				1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
DILATATION/DUCTS	4 (8%)	11 (22%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MULTIPLE CYSTS				1 (2%)
CYSTIC DUCTS	1 (2%)	1 (2%)		1 (2%)
HEMORRHAGE		1 (2%)		
HYPERPLASIA, CYSTIC	1 (2%)		2 (4%)	
*MAMMARY ACINUS	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		
HYPERPLASIA, CYSTIC	8 (16%)		15 (30%)	5 (10%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)			
#PROSTATE	(49)	(48)	(49)	(48)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	6 (12%)	3 (6%)	2 (4%)	2 (4%)
ATROPHY, FOCAL	1 (2%)		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
DEGENERATION, NOS		1 (2%)		
#TESTIS	(50)	(50)	(49)	(50)
MINERALIZATION			1 (2%)	
HEMORRHAGIC CYST		1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
DEGENERATION, NOS	1 (2%)			
ATROPHY, NOS	1 (2%)			
HYPERPLASIA, INTERSTITIAL CELL	8 (16%)	9 (18%)	5 (10%)	6 (12%)
#TESTIS/TUBULE	(50)	(50)	(49)	(50)
MINERALIZATION			1 (2%)	
DEGENERATION, NOS	44 (88%)	41 (82%)	40 (82%)	39 (78%)
ATROPHY, FOCAL	1 (2%)	1 (2%)	4 (8%)	
ATROPHY, DIFFUSE	2 (4%)			
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
HEMATOMA, ORGANIZED			1 (2%)	
#CEREBRUM	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE				1 (2%)
ATROPHY, PRESSURE	1 (2%)		1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
NECROSIS, HEMORRHAGIC			1 (2%)	
#MEDULLA OBLONGATA	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
SPECIAL SENSE ORGANS				
*EYE ANTERIOR CHAMBER	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
*EYE POSTERIOR CHAMBE	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
*EYE/CORNEA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)			
*EYE/IRIS	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)		
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	6 (12%)	5 (10%)	1 (2%)	2 (4%)
ATROPHY, NOS	2 (4%)			
ATROPHY, FOCAL	3 (6%)		1 (2%)	2 (4%)
ATROPHY, DIFFUSE	1 (2%)			
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)
CATARACT	6 (12%)	5 (10%)	2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM				
*CARTILAGE,NOS	(50)	(50)	(50)	(50)
ECTOPIA	1 (2%)			
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS				2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE		1 (2%)		
*MEDIASTINAL PLEURA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FIBRINOUS				1 (2%)
*EPICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FIBRINOUS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
HYPERPLASIA, FOCAL				1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MINERALIZATION	1 (2%)			
DEGENERATION, NOS		1 (2%)		
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF			1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS MISSING	1			
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
HYPERKERATOSIS			1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING				1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		1 (2%)	1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(47)	(49)	(49)	(49)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
#TRACHEAL SUBMUCOSA	(47)	(49)	(49)	(49)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#LUNG	(49)	(49)	(50)	(50)
ASPIRATION, FOREIGN BODY			5 (10%)	9 (18%)
CONGESTION, NOS	1 (2%)			
EDEMA, NOS			1 (2%)	
HEMORRHAGE				1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)	
PNEUMONIA, ASPIRATION			1 (2%)	
LOBAR PNEUMONIA, ACUTE			1 (2%)	
INFLAMMATION, ACUTE FOCAL		2 (4%)		1 (2%)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	1 (2%)	7 (14%)	11 (22%)
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)			
GRANULOMA, NOS		1 (2%)		1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU		14 (29%)	8 (16%)	2 (4%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
EOSINOPHILIC GRANULOMA	1 (2%)			
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(48)	(48)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)			
HYPERPLASIA, GRANULOCYTIC		3 (6%)		2 (4%)
HYPERPLASIA, EOSINOPHILIC	1 (2%)			
HYPERPLASIA, RETICULUM CELL	4 (8%)		2 (4%)	6 (12%)
HYPOPLASIA, HEMATOPOIETIC	1 (2%)			
#SPLEEN	(49)	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	2 (4%)			1 (2%)
LYMPHOID DEPLETION	1 (2%)			
HYPERPLASIA, RETICULUM CELL	1 (2%)			
#SPLENIC RED PULP	(49)	(50)	(50)	(50)
PIGMENTATION, NOS	14 (29%)		1 (2%)	1 (2%)
HEMATOPOIESIS				1 (2%)
#MANDIBULAR L. NODE	(47)	(45)	(40)	(40)
CONGESTION, NOS	11 (23%)		2 (5%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (3%)	1 (3%)
PIGMENTATION, NOS	1 (2%)			
HISTIOCYTOSIS			1 (3%)	1 (3%)
PLASMACYTOSIS	1 (2%)			
HYPERPLASIA, RETICULUM CELL		3 (7%)	1 (3%)	
HYPERPLASIA, LYMPHOID				1 (3%)
#LYMPH NODE OF THORAX	(47)	(45)	(40)	(40)
CONGESTION, NOS				1 (3%)
HEMORRHAGE			1 (3%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			1 (3%)
LYMPHOID DEPLETION			1 (3%)	
HYPERPLASIA, RETICULUM CELL	1 (2%)			1 (3%)
#PANCREATIC L.NODE	(47)	(45)	(40)	(40)
INFLAMMATION, FOCAL GRANULOMATOU			1 (3%)	
#MESENTERIC L. NODE	(47)	(45)	(40)	(40)
INFLAMMATION, MULTIFOCAL			1 (3%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
HYPERPLASIA, RETICULUM CELL	1 (2%)			
#RENAL LYMPH NODE	(47)	(45)	(40)	(40)
INFLAMMATION, ACUTE		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
GRANULOMA, NOS			2 (5%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (3%)	
*FEMUR	(49)	(50)	(50)	(50)
HYPERPLASIA, RETICULUM CELL				1 (2%)
#PEYER'S PATCH	(48)	(48)	(48)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)	
#THYMUS	(46)	(45)	(46)	(48)
HEMORRHAGE				1 (2%)
NECROSIS, NOS		1 (2%)		
NECROSIS, DIFFUSE				1 (2%)
LYMPHOID DEPLETION		1 (2%)		
#THYMIC CORTEX	(46)	(45)	(46)	(48)
LYMPHOID DEPLETION		1 (2%)	2 (4%)	
#PANCREATIC ISLETS	(46)	(50)	(49)	(49)
HYPERPLASIA, EOSINOPHILIC				1 (2%)
CIRCULATORY SYSTEM				
#RIGHT ATRIUM	(49)	(50)	(50)	(50)
EMBRYONAL REST	1 (2%)			
#MYOCARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
DEGENERATION, NOS	36 (73%)	22 (44%)	32 (64%)	39 (78%)
*CORONARY ARTERY	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
#HEPATIC SINUSOID	(49)	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		2 (4%)	
DIGESTIVE SYSTEM				
*MUCOSA OF TONGUE	(49)	(50)	(50)	(50)
HYPERKERATOSIS	1 (2%)			
ACANTHOSIS	1 (2%)			
#LIVER	(49)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, FOCAL GRANULOMATOU	23 (47%)	21 (42%)	11 (22%)	11 (22%)
DEGENERATION, CYSTIC	3 (6%)		1 (2%)	2 (4%)
NECROSIS, FOCAL				5 (10%)
CYTOPLASMIC CHANGE, NOS				2 (4%)
CYTOPLASMIC VACUOLIZATION				1 (2%)
BASOPHILIC CYTO CHANGE	38 (78%)	27 (54%)	18 (36%)	10 (20%)
FOCAL CELLULAR CHANGE				1 (2%)
EOSINOPHILIC CYTO CHANGE	1 (2%)	1 (2%)		
CLEAR-CELL CHANGE	3 (6%)	1 (2%)		2 (4%)
ANGIECTASIS				1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)		
CONGESTION, ACUTE		1 (2%)		
CONGESTION, PASSIVE				1 (2%)
DEGENERATION, NOS	1 (2%)	1 (2%)		
NECROSIS, FOCAL			1 (2%)	2 (4%)
#LIVER/PERIPORTAL	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
CYTOPLASMIC VACUOLIZATION				1 (2%)
#BILE DUCT	(49)	(50)	(50)	(50)
HYPERPLASIA, FOCAL	11 (22%)	20 (40%)	16 (32%)	6 (12%)
#PANCREAS	(46)	(50)	(49)	(49)
DILATATION/DUCTS			1 (2%)	
#PANCREATIC DUCT	(46)	(50)	(49)	(49)
MULTIPLE CYSTS	1 (2%)			
#PANCREATIC ACINUS	(46)	(50)	(49)	(49)
NUCLEAR ENLARGEMENT			1 (2%)	
CYTOMEGALY			1 (2%)	
ATROPHY, FOCAL	9 (20%)	6 (12%)	5 (10%)	5 (10%)
ATROPHY, DIFFUSE		1 (2%)		
#ESOPHAGUS	(49)	(50)	(50)	(50)
PENETRATING WOUND		2 (4%)		
DILATATION, NOS		2 (4%)	1 (2%)	1 (2%)
NECROSIS, FOCAL		1 (2%)		
#ESOPHAGEAL MUCOUS ME	(49)	(50)	(50)	(50)
NECROSIS, FOCAL		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PERIESOPHAGEAL TISSU	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
#GASTRIC MUCOSA	(49)	(50)	(49)	(50)
NECROSIS, FOCAL			1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)	
#CARDIAC STOMACH	(49)	(50)	(49)	(50)
ULCER, FOCAL		1 (2%)		
#COLON	(48)	(50)	(47)	(50)
PARASITISM	1 (2%)			1 (2%)
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
NEPHROPATHY	30 (61%)	7 (14%)	18 (36%)	30 (60%)
HYPERPLASIA, TUBULAR CELL	1 (2%)			
#KIDNEY/CORTEX	(49)	(50)	(50)	(50)
MULTIPLE CYSTS				1 (2%)
#KIDNEY/MEDULLA	(49)	(50)	(50)	(50)
MINERALIZATION	1 (2%)	1 (2%)		
CYST, NOS			1 (2%)	
#KIDNEY/TUBULE	(49)	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)	
PIGMENTATION, NOS	2 (4%)		1 (2%)	4 (8%)
#KIDNEY/PELVIS	(49)	(50)	(50)	(50)
MINERALIZATION			3 (6%)	
#U.BLADDER/SUBMUCOSA	(45)	(47)	(46)	(48)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(48)	(46)	(46)	(43)
EMBRYONAL DUCT CYST				2 (5%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, FOCAL	1 (2%)	4 (9%)	2 (4%)	2 (5%)
#ANTERIOR PITUITARY	(48)	(46)	(46)	(43)
EMBRYONAL DUCT CYST				7 (16%)
CYST, NOS		1 (2%)		
HEMORRHAGIC CYST		1 (2%)	1 (2%)	
HEMORRHAGE, CHRONIC				1 (2%)
DEGENERATION, CYSTIC	1 (2%)	1 (2%)		
CHOLESTEROL DEPOSIT				1 (2%)
#ADRENAL	(49)	(49)	(49)	(49)
PIGMENTATION, NOS	1 (2%)			
#ADRENAL CORTEX	(49)	(49)	(49)	(49)
DEGENERATION, NOS	1 (2%)			
NECROSIS, FOCAL				3 (6%)
NECROSIS, DIFFUSE				1 (2%)
METAMORPHOSIS FATTY		2 (4%)		
LIPOIDOSIS	8 (16%)		2 (4%)	4 (8%)
HYPERPLASIA, FOCAL		1 (2%)		
#ZONA FASCICULATA	(49)	(49)	(49)	(49)
CONGESTION, NOS			1 (2%)	
NECROSIS, FOCAL		1 (2%)	1 (2%)	
LIPOIDOSIS			2 (4%)	
HYPERTROPHY, FOCAL	1 (2%)			
#ZONA RETICULARIS	(49)	(49)	(49)	(49)
NECROSIS, FOCAL			1 (2%)	
NUCLEAR ENLARGEMENT				1 (2%)
#ADRENAL MEDULLA	(49)	(49)	(49)	(49)
HYPERPLASIA, FOCAL	3 (6%)	4 (8%)	2 (4%)	2 (4%)
ANGIECTASIS		1 (2%)		
#THYROID	(49)	(49)	(49)	(49)
EMBRYONAL DUCT CYST		1 (2%)		
FOLLICULAR CYST, NOS		1 (2%)	2 (4%)	2 (4%)
ATROPHY, NOS				1 (2%)
HYPERPLASIA, C-CELL	33 (67%)	16 (33%)	20 (41%)	19 (39%)
#THYROID CAPSULE	(49)	(49)	(49)	(49)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
#PANCREATIC ISLETS	(46)	(50)	(49)	(49)
HYPERPLASIA, FOCAL			1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)	16 (32%)	10 (20%)	4 (8%)
CYST, NOS	2 (4%)	1 (2%)		
MULTIPLE CYSTS			1 (2%)	
*MAMMARY ACINUS	(49)	(50)	(50)	(50)
DILATATION, NOS		3 (6%)		
HYPERPLASIA, FOCAL	1 (2%)	3 (6%)		
HYPERPLASIA, CYSTIC	26 (53%)	2 (4%)	10 (20%)	19 (38%)
*CLITORAL GLAND	(49)	(50)	(50)	(50)
CYST, NOS			1 (2%)	
#UTERUS	(49)	(50)	(49)	(50)
DILATATION, NOS	5 (10%)	1 (2%)	7 (14%)	6 (12%)
HEMORRHAGE				1 (2%)
#CERVICAL MUCOUS MEMB	(49)	(50)	(49)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
FIBROSIS, MULTIFOCAL			3 (6%)	
FIBROSIS, DIFFUSE		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	14 (29%)	14 (28%)	6 (12%)	10 (20%)
#ENDOMETRIAL GLAND	(49)	(50)	(49)	(50)
CYST, NOS		1 (2%)		
MULTIPLE CYSTS	2 (4%)		1 (2%)	2 (4%)
#OVARY/PAROVARIAN	(49)	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
#OVARY	(49)	(50)	(49)	(50)
FOLLICULAR CYST, NOS	2 (4%)	1 (2%)	3 (6%)	1 (2%)
CORPUS LUTEUM CYST	1 (2%)			
CYSTIC DUCTS			1 (2%)	
PAROVARIAN CYST	2 (4%)	7 (14%)	1 (2%)	
HEMORRHAGIC CYST			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)	
ATROPHY, SENILE	5 (10%)		2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MESOVARIUM	(49)	(50)	(49)	(50)
NECROSIS, FAT				1 (2%)
#OVARY/FOLLICLE	(49)	(50)	(49)	(50)
MULTIPLE CYSTS				1 (2%)
NERVOUS SYSTEM				
#LATERAL VENTRICLE	(49)	(50)	(50)	(50)
HYDROCEPHALUS, NOS	2 (4%)			
#CEREBRUM	(49)	(50)	(50)	(50)
COMPRESSION			1 (2%)	
HEMORRHAGE				1 (2%)
ATROPHY, PRESSURE	8 (16%)	2 (4%)		2 (4%)
#BRAIN	(49)	(50)	(50)	(50)
HYDROCEPHALUS, NOS		2 (4%)		
ATROPHY, PRESSURE		1 (2%)		
#BRAIN/THALAMUS	(49)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
#MEDULLA OBLONGATA	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
SPECIAL SENSE ORGANS				
*EYE/RETINA	(49)	(50)	(50)	(50)
DEGENERATION, NOS	3 (6%)	1 (2%)	3 (6%)	3 (6%)
ATROPHY, NOS	1 (2%)			1 (2%)
ATROPHY, FOCAL	1 (2%)		1 (2%)	2 (4%)
ATROPHY, DIFFUSE	1 (2%)	1 (2%)	1 (2%)	
*EYE/CRYSTALLINE LENS	(49)	(50)	(50)	(50)
CATARACT	3 (6%)	1 (2%)	2 (4%)	2 (4%)
MUSCULOSKELETAL SYSTEM				
*FEMUR	(49)	(50)	(50)	(50)
OSTEOSCLEROSIS	1 (2%)	3 (6%)	2 (4%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*MEDIASTINUM	(49)	(50)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
EDEMA, NOS				1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
*PLEURA	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)		
*MEDIASTINAL PLEURA	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE		4 (8%)	1 (2%)	
INFLAMMATION, ACUTE DIFFUSE			1 (2%)	
INFLAMMATION, ACUTE FIBRINOUS		1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)	
*PERICARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)		
INFLAMMATION, ACUTE DIFFUSE		1 (2%)		
INFLAMMATION, ACUTE FIBRINOUS		1 (2%)	1 (2%)	
*EPICARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)		
INFLAMMATION, ACUTE DIFFUSE		1 (2%)		
INFLAMMATION, ACUTE FIBRINOUS		1 (2%)	1 (2%)	
*MESENTERY	(49)	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			3 (6%)
NECROSIS, FAT	1 (2%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	
ANIMAL MISSING/NO NECROPSY	1			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)		
INFLAMMATION, ACUTE DIFFUSE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
EROSION			1 (2%)	
FIBROSIS, FOCAL		1 (2%)		
FIBROSIS, MULTIFOCAL		1 (2%)		
PARASITISM			1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
ABSCESS, CHRONIC	1 (2%)		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
FIBROSIS, FOCAL		1 (2%)		
NECROSIS, FOCAL	1 (2%)			
NECROSIS, FAT		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG/BRONCHIOLE	(50)	(50)	(49)	(49)
HYPERPLASIA, EPITHELIAL				1 (2%)
#LUNG	(50)	(50)	(49)	(49)
ECTOPIA	1 (2%)			
EDEMA, NOS	1 (2%)			
HEMORRHAGE				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	1 (2%)		
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)		2 (4%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)			1 (2%)
INFLAMMATION, PYOGRANULOMATOUS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
FOREIGN MATERIAL, NOS			2 (4%)	
HEMOSIDEROSIS	1 (2%)			
ALVEOLAR MACROPHAGES			2 (4%)	4 (8%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	5 (10%)		1 (2%)	2 (4%)
HISTIOCYTOSIS			1 (2%)	
#LUNG/ALVEOLI	(50)	(50)	(49)	(49)
FOREIGN MATERIAL, NOS				1 (2%)
HEMOSIDEROSIS			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
#BONE MARROW	(49)	(48)	(48)	(48)
HYPERPLASIA, NEUTROPHILIC			1 (2%)	
#SPLEEN	(48)	(49)	(49)	(47)
LYMPHOID DEPLETION				2 (4%)
HYPERPLASIA, LYMPHOID	1 (2%)			
HEMATOPOIESIS			2 (4%)	1 (2%)
#SPLENIC FOLLICLES	(48)	(49)	(49)	(47)
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL	1 (2%)			
LYMPHOID DEPLETION			1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
#SPLENIC RED PULP	(48)	(49)	(49)	(47)
HEMATOPOIESIS			2 (4%)	1 (2%)
#LYMPH NODE	(34)	(32)	(32)	(38)
NECROSIS, NOS			1 (3%)	
#MANDIBULAR L. NODE	(34)	(32)	(32)	(38)
EDEMA, NOS	1 (3%)			
HYPERPLASIA, FOCAL				1 (3%)
#MEDIASTINAL L.NODE	(34)	(32)	(32)	(38)
HYPERPLASIA, LYMPHOID				1 (3%)
#PANCREATIC L.NODE	(34)	(32)	(32)	(38)
HYPERPLASIA, RETICULUM CELL			1 (3%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MESENTERIC L. NODE	(34)	(32)	(32)	(38)
HEMORRHAGE		3 (9%)		2 (5%)
HYPERPLASIA, RETICULUM CELL			8 (25%)	10 (26%)
HYPERPLASIA, LYMPHOID				2 (5%)
#LUNG	(50)	(50)	(49)	(49)
LEUKOCYTOSIS, NOS	2 (4%)			
HYPERPLASIA, LYMPHOID				1 (2%)
#THYMUS	(32)	(33)	(25)	(31)
NECROSIS, NOS				1 (3%)
LYMPHOID DEPLETION	1 (3%)		4 (16%)	
#THYMIC MEDULLA	(32)	(33)	(25)	(31)
HYPERPLASIA, EPITHELIAL	1 (3%)			
HYPERPLASIA, LYMPHOID			1 (4%)	
#THYMIC LYMPHOCYTES	(32)	(33)	(25)	(31)
NECROSIS, DIFFUSE	1 (3%)			1 (3%)
CIRCULATORY SYSTEM				
#MESENTERIC L. NODE	(34)	(32)	(32)	(38)
LYMPHANGIECTASIS				1 (3%)
#TRACHEA	(46)	(41)	(48)	(48)
PERIARTERITIS				1 (2%)
#LUNG	(50)	(50)	(49)	(49)
PERIVASCULITIS		1 (2%)		
#HEART	(50)	(50)	(49)	(49)
ENDOCARDITIS, BACTERIAL	1 (2%)			
PERIVASCULITIS		1 (2%)		
#HEART/ATRIUM	(50)	(50)	(49)	(49)
THROMBUS, MURAL		1 (2%)		
#HEART/VENTRICLE	(50)	(50)	(49)	(49)
THROMBUS, ORGANIZED				1 (2%)
#MYOCARDIUM	(50)	(50)	(49)	(49)
MINERALIZATION	1 (2%)		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)	2 (4%)
FIBROSIS, MULTIFOCAL	1 (2%)			
DEGENERATION, NOS		1 (2%)		
#MYOCARDIUM OF LEFT V	(50)	(50)	(49)	(49)
PERIVASCULITIS	1 (2%)			
*CORONARY ARTERY	(50)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
*RENAL ARTERY	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
*MESENTERY	(50)	(50)	(50)	(50)
THROMBUS, ORGANIZED	1 (2%)			
PERIARTERITIS				1 (2%)
#KIDNEY	(50)	(50)	(50)	(48)
EMBOLUS, SEPTIC	1 (2%)			
PERIVASCULITIS		1 (2%)		
#PROSTATE	(45)	(50)	(49)	(48)
PERIVASCULITIS	1 (2%)	1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(48)	(49)	(50)	(48)
CYST, NOS				1 (2%)
GRANULOMA, FOREIGN BODY				1 (2%)
#SALIVARY GLAND INTER	(48)	(49)	(50)	(48)
INFLAMMATION, ACUTE FOCAL				1 (2%)
#LIVER	(50)	(50)	(49)	(48)
HEMORRHAGE, CHRONIC				1 (2%)
INFLAMMATION, ACUTE FOCAL	2 (4%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
NECROSIS, FOCAL	5 (10%)	5 (10%)		1 (2%)
NECROSIS, ISCHEMIC				1 (2%)
CYTOPLASMIC VACUOLIZATION		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BASOPHILIC CYTO CHANGE	1 (2%)			
FOCAL CELLULAR CHANGE	2 (4%)	1 (2%)	2 (4%)	
REGENERATIVE NODULE				1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(49)	(48)
NECROSIS, NOS	1 (2%)	1 (2%)		
NECROSIS, FOCAL	1 (2%)			1 (2%)
NECROSIS, DIFFUSE				1 (2%)
CYTOPLASMIC VACUOLIZATION				1 (2%)
#LIVER/HEPATOCYTES	(50)	(50)	(49)	(48)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			2 (4%)	
NECROSIS, NOS	1 (2%)			
NECROSIS, FOCAL			4 (8%)	2 (4%)
NECROSIS, COAGULATIVE			3 (6%)	1 (2%)
NECROSIS, ISCHEMIC			1 (2%)	
NUCLEAR ENLARGEMENT				1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		1 (2%)	
BASOPHILIC CYTO CHANGE				1 (2%)
FOCAL CELLULAR CHANGE				1 (2%)
CELL-SIZE, ALTERATION				2 (4%)
REGENERATION, NOS				1 (2%)
*GALLBLADDER	(50)	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)	
#BILE DUCT	(50)	(50)	(49)	(48)
DILATATION, NOS			1 (2%)	
#PANCREAS	(47)	(49)	(47)	(48)
CYSTIC DUCTS		1 (2%)		
NECROSIS, FOCAL				1 (2%)
#PANCREATIC ACINUS	(47)	(49)	(47)	(48)
NECROSIS, FOCAL			1 (2%)	
ATROPHY, NOS			1 (2%)	
ATROPHY, FOCAL			1 (2%)	
ATROPHY, DIFFUSE		1 (2%)		
#PANCREATIC INTERSTIT	(47)	(49)	(47)	(48)
INFLAMMATION, ACUTE			1 (2%)	
#ESOPHAGEAL MUSCULARI	(48)	(48)	(49)	(49)
REGENERATION, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CARDIAC STOMACH	(47)	(48)	(46)	(46)
ULCER, ACUTE	1 (2%)			
INFLAMMATION, ACUTE FOCAL			1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)			
#GASTRIC FUNDUS	(47)	(48)	(46)	(46)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
HYPERPLASIA, EPITHELIAL		1 (2%)		
#JEJUNAL SUBMUCOSA	(43)	(45)	(40)	(42)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
#COLON	(46)	(47)	(41)	(47)
NEMATODIASIS	1 (2%)			3 (6%)
PARASITISM			2 (5%)	
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(48)
ECTOPIA		2 (4%)		
MINERALIZATION	2 (4%)	3 (6%)		1 (2%)
HYDRONEPHROSIS		1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	5 (10%)	19 (38%)		5 (10%)
GLOMERULONEPHRITIS, MEMBRANOUS				1 (2%)
PYELONEPHRITIS, ACUTE				1 (2%)
GLOMERULONEPHRITIS, SUBACUTE		1 (2%)		
PYELONEPHRITIS, ACUTE/CHRONIC		1 (2%)	1 (2%)	
NEPHROPATHY	4 (8%)	3 (6%)		
NECROSIS, FOCAL				1 (2%)
INFARCT, FOCAL		1 (2%)		
INFARCT, HEALED			2 (4%)	
BASEMENT MEMBRANE, ALTERATION		1 (2%)		
ANGIECTASIS		1 (2%)		
#KIDNEY/CORTEX	(50)	(50)	(50)	(48)
ECTOPIA				3 (6%)
MINERALIZATION		1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
FIBROSIS, FOCAL	1 (2%)			
INFARCT, FOCAL			1 (2%)	
METAPLASIA, OSSEOUS			1 (2%)	
#PERIRENAL TISSUE	(50)	(50)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#KIDNEY/GLOMERULUS	(50)	(50)	(50)	(48)
INFLAMMATION ACTIVE CHRONIC		1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
#BOWMAN'S CAPSULE	(50)	(50)	(50)	(48)
DILATATION, NOS	1 (2%)			
#KIDNEY/TUBULE	(50)	(50)	(50)	(48)
MINERALIZATION				1 (2%)
DILATATION, NOS	2 (4%)	2 (4%)		2 (4%)
MULTIPLE CYSTS	1 (2%)			
DEGENERATION, NOS				1 (2%)
NECROSIS, FOCAL			1 (2%)	
NECROSIS, DIFFUSE			1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)	
METAPLASIA, OSSEOUS			1 (2%)	
REGENERATION, NOS	15 (30%)	23 (46%)	8 (16%)	14 (29%)
#KIDNEY/PELVIS	(50)	(50)	(50)	(48)
INFLAMMATION, ACUTE	2 (4%)			
*PERIURETERAL TISSUE	(50)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)
#URINARY BLADDER	(47)	(47)	(42)	(47)
DILATATION, NOS				1 (2%)
CAST, NOS	2 (4%)			2 (4%)
INFLAMMATION, ACUTE NECROTIZING	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)	
NECROSIS, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)	
*URETHRA	(50)	(50)	(50)	(50)
OBSTRUCTION, NOS				1 (2%)
*PROSTATIC URETHRA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)			
HYPERPLASIA, EPITHELIAL			2 (4%)	
ENDOCRINE SYSTEM				
#PITUITARY	(39)	(41)	(33)	(40)
EMBRYONAL DUCT CYST	1 (3%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, EPITHELIAL	1 (3%)			
#ADRENAL CORTEX	(46)	(50)	(47)	(47)
LIPOIDOSIS		1 (2%)		
FOCAL CELLULAR CHANGE				6 (13%)
HYPERTROPHY, FOCAL	7 (15%)	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)	2 (4%)
#ZONA FASCICULATA	(46)	(50)	(47)	(47)
FOCAL CELLULAR CHANGE			3 (6%)	
HYPERTROPHY, FOCAL	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL MEDULLA	(46)	(50)	(47)	(47)
FIBROSIS, DIFFUSE		1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)	2 (4%)	1 (2%)	
#THYROID	(42)	(39)	(47)	(42)
COLLOID CYST				1 (2%)
#PANCREATIC ISLETS	(47)	(49)	(47)	(48)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	2 (4%)			
REPRODUCTIVE SYSTEM				
*PREPUCE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE				1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
ABSCESS, CHRONIC			2 (4%)	1 (2%)
INFLAMMATION, PYOGRANULOMATOUS				1 (2%)
#PROSTATE	(45)	(50)	(49)	(48)
INFLAMMATION, ACUTE	1 (2%)			1 (2%)
INFLAMMATION ACTIVE CHRONIC				1 (2%)
INFLAMMATION, CHRONIC			1 (2%)	
#TESTIS	(48)	(50)	(48)	(49)
ATROPHY, NOS		1 (2%)		
HYPOSPERMATOGENESIS		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#TESTIS/TUBULE	(48)	(50)	(48)	(49)
MINERALIZATION	1 (2%)			
ATROPHY, FOCAL		1 (2%)		
#SPERMATOGENIC EPITHE	(48)	(50)	(48)	(49)
DEGENERATION, NOS			1 (2%)	
ATROPHY, DIFFUSE			1 (2%)	
*EPIDIDYMIS	(50)	(50)	(50)	(50)
GRANULOMA, NOS	1 (2%)	1 (2%)		
GRANULOMA, SPERMATIC			1 (2%)	
NECROSIS, FAT				1 (2%)
METAPLASIA, SQUAMOUS		1 (2%)		
NERVOUS SYSTEM				
#LATERAL VENTRICLE	(50)	(50)	(50)	(50)
PIGMENTATION, NOS			1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
MINERALIZATION	18 (36%)	25 (50%)		
HYDROCEPHALUS, NOS		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
#BRAIN/THALAMUS	(50)	(50)	(50)	(50)
MINERALIZATION			17 (34%)	23 (46%)
#HYPOTHALAMUS	(50)	(50)	(50)	(50)
ATROPHY, PRESSURE				1 (2%)
*SCIATIC NERVE	(50)	(50)	(50)	(50)
DEGENERATION, NOS			1 (2%)	
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY	2 (4%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES				
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
NECROSIS, FAT				1 (2%)
*PERITONEUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
*PARIETAL PERITONEUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
*PERICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
ALL OTHER SYSTEMS				
PERIORBITAL REGION				
MULTIPLE CYSTS	1			
ADIPOSE TISSUE				
INFLAMMATION, ACUTE/CHRONIC		1		
MESENTERY OF COLON				
INFLAMMATION, ACUTE FOCAL			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED			1	
AUTO/NECROPSY/HISTO PERF	1			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED CHLOROBENZENE IN CORN OIL BY GAVAGE

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMORRHAGE, CHRONIC				1 (2%)
RESPIRATORY SYSTEM				
#BRONCHIAL SUBMUCOSA	(49)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)			
#LUNG	(49)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	16 (32%)	3 (6%)	5 (10%)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
FOREIGN MATERIAL, NOS				1 (2%)
ALVEOLAR MACROPHAGES	5 (10%)		1 (2%)	1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)		1 (2%)	4 (8%)
#LUNG/ALVEOLI	(49)	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(50)	(49)	(50)
ATROPHY, FOCAL				1 (2%)
#SPLEEN	(47)	(50)	(49)	(49)
HYPERPLASIA, LYMPHOID		3 (6%)		1 (2%)
HEMATOPOIESIS			1 (2%)	2 (4%)
#SPLENIC FOLLICLES	(47)	(50)	(49)	(49)
NECROSIS, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID	4 (9%)		5 (10%)	5 (10%)
#SPLENIC RED PULP	(47)	(50)	(49)	(49)
HEMATOPOIESIS			1 (2%)	
#LYMPH NODE	(36)	(33)	(42)	(34)
HYPERPLASIA, LYMPHOID		1 (3%)		
#MANDIBULAR L. NODE	(36)	(33)	(42)	(34)
PLASMACYTOSIS			1 (2%)	
#LYMPH NODE OF THORAX	(36)	(33)	(42)	(34)
HYPERPLASIA, LYMPHOID				1 (3%)
#MESENTERIC L. NODE	(36)	(33)	(42)	(34)
HYPERPLASIA, RETICULUM CELL			2 (5%)	1 (3%)
HEMATOPOIESIS				1 (3%)
#BRONCHIAL SUBMUCOSA	(49)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
#LUNG	(49)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	6 (12%)			1 (2%)
#KIDNEY	(46)	(50)	(50)	(50)
MASTOCYTOSIS			1 (2%)	
#THYMUS	(41)	(42)	(41)	(38)
HEMATOPOIESIS			1 (2%)	
#THYMIC CORTEX	(41)	(42)	(41)	(38)
NECROSIS, NOS			1 (2%)	
#THYMIC MEDULLA	(41)	(42)	(41)	(38)
HYPERPLASIA, LYMPHOID				1 (3%)
#THYMIC LYMPHOCYTES	(41)	(42)	(41)	(38)
NECROSIS, NOS			1 (2%)	
CIRCULATORY SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
PERIVASCULITIS				1 (2%)
#MESENTERIC L. NODE	(36)	(33)	(42)	(34)
THROMBOSIS, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PERITRACHEAL TISSUE	(45)	(45)	(45)	(47)
PERIVASCULITIS				1 (2%)
#HEART/ATRIUM	(50)	(50)	(50)	(50)
THROMBUS, MURAL		1 (2%)		
#MYOCARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
FIBROSIS, FOCAL			1 (2%)	
#MYOCARDIUM OF LEFT V	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
#CARDIAC VALVE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
DEGENERATION, MUCOID			1 (2%)	
*AORTA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
*AORTIC TUNICA ADVENT	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
*CORONARY ARTERY	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
*PULMONARY VEIN	(50)	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
EMBOLUS, FAT			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(48)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE FOCAL	10 (21%)	3 (6%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC	4 (8%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
NECROSIS, FOCAL		9 (18%)		
HEMOSIDEROSIS		1 (2%)		
BASOPHILIC CYTO CHANGE		1 (2%)		
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(50)	(50)	(50)
NECROSIS, FOCAL	2 (4%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REGENERATION, NOS	1 (2%)			
#LIVER/HEPATOCYTES	(48)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	3 (6%)
NECROSIS, FOCAL	2 (4%)		5 (10%)	2 (4%)
NECROSIS, COAGULATIVE				3 (6%)
BASOPHILIC CYTO CHANGE	1 (2%)			
CLEAR-CELL CHANGE				1 (2%)
CELL-SIZE, ALTERATION				2 (4%)
#PANCREAS	(44)	(47)	(50)	(47)
DILATATION/DUCTS			1 (2%)	
CYSTIC DUCTS				1 (2%)
#PANCREATIC DUCT	(44)	(47)	(50)	(47)
MULTIPLE CYSTS	1 (2%)	1 (2%)		
#PANCREATIC ACINUS	(44)	(47)	(50)	(47)
NECROSIS, FOCAL	1 (2%)			
ATROPHY, NOS	1 (2%)	1 (2%)		
ATROPHY, FOCAL	2 (5%)	2 (4%)	1 (2%)	
ATROPHY, DIFFUSE			1 (2%)	
#PANCREATIC INTERSTIT	(44)	(47)	(50)	(47)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
#ESOPHAGUS	(50)	(48)	(49)	(48)
NECROSIS, FOCAL			1 (2%)	1 (2%)
#ESOPHAGEAL MUSCULARI	(50)	(48)	(49)	(48)
REGENERATION, NOS				1 (2%)
#ESOPHAGEAL ADVENTITI	(50)	(48)	(49)	(48)
GRANULOMA, NOS				1 (2%)
#GASTRIC SUBMUCOSA	(48)	(47)	(49)	(46)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
#CARDIAC STOMACH	(48)	(47)	(49)	(46)
ULCER, FOCAL		1 (2%)		
ULCER, ACUTE		1 (2%)		
EROSION				1 (2%)
#COLON	(46)	(49)	(48)	(47)
NEMATODIASIS	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(46)	(50)	(50)	(50)
ECTOPIA		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	11 (24%)	20 (40%)	5 (10%)	3 (6%)
GLOMERULONEPHRITIS, MEMBRANOUS			3 (6%)	
NEPHROPATHY		1 (2%)		
METAPLASIA, OSSEOUS			4 (8%)	
#KIDNEY/CORTEX	(46)	(50)	(50)	(50)
CYST, NOS		1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
#RENAL CORTICAL INTER	(46)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			3 (6%)
#KIDNEY/GLOMERULUS	(46)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
#KIDNEY/TUBULE	(46)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
DEGENERATION, NOS			3 (6%)	
DEGENERATION, CYSTIC			1 (2%)	
DEGENERATION, GRANULAR			1 (2%)	
DEGENERATION, HYALINE		1 (2%)		
NECROSIS, FOCAL	1 (2%)			1 (2%)
CYTOPLASMIC CHANGE, NOS	1 (2%)			
CELL-SIZE, ALTERATION			1 (2%)	
REGENERATION, NOS	5 (11%)	1 (2%)	1 (2%)	
#U.BLADDER/SUBMUCOSA	(44)	(45)	(46)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(41)	(39)	(38)	(38)
HYPERPLASIA, FOCAL		1 (3%)		
HYPERPLASIA, CHROMOPHOBE-CELL		2 (5%)		
#ANTERIOR PITUITARY	(41)	(39)	(38)	(38)
HYPERPLASIA, CHROMOPHOBE-CELL		1 (3%)	4 (11%)	3 (8%)
#ADRENAL CORTEX	(49)	(49)	(50)	(49)
CYST, NOS		1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
DEGENERATION, NOS				1 (2%)
LIPOIDOSIS		1 (2%)		
#ZONA RETICULARIS	(49)	(49)	(50)	(49)
DEGENERATION, NOS			1 (2%)	
NECROSIS, FOCAL				1 (2%)
METAMORPHOSIS FATTY		2 (4%)		
ANGIECTASIS				1 (2%)
#ADRENAL MEDULLA	(49)	(49)	(50)	(49)
HYPERPLASIA, FOCAL		1 (2%)		
#THYROID	(40)	(42)	(43)	(44)
CYSTIC FOLLICLES	2 (5%)			
FOLLICULAR CYST, NOS			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS	1 (3%)			
HYPERPLASIA, FOLLICULAR-CELL				1 (2%)
#PARATHYROID	(22)	(21)	(23)	(23)
THYROGLOSSAL DUCT CYST	1 (5%)			
#PANCREATIC ISLETS	(44)	(47)	(50)	(47)
HYPERPLASIA, FOCAL		1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
MULTIPLE CYSTS			1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	2 (4%)		1 (2%)	
#UTERUS	(48)	(50)	(50)	(48)
CYST, NOS		1 (2%)		
MULTILOCULAR CYST		1 (2%)		
INFLAMMATION, ACUTE		1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
GRANULOMA, NOS		1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(50)	(50)	(48)
HEMORRHAGE	1 (2%)			
INFLAMMATION, ACUTE DIFFUSE			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, PAPILLARY	1 (2%)			
#ENDOMETRIAL GLAND	(48)	(50)	(50)	(48)
FOLLICULAR CYST, NOS	1 (2%)			
MULTIPLE CYSTS	5 (10%)	4 (8%)	2 (4%)	4 (8%)
HYPERPLASIA, CYSTIC	36 (75%)	38 (76%)	46 (92%)	37 (77%)
#OVARY/PAROVARIAN	(40)	(47)	(43)	(45)
MINERALIZATION	1 (3%)			
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
#OVARY	(40)	(47)	(43)	(45)
CYST, NOS		7 (15%)	1 (2%)	
FOLLICULAR CYST, NOS	17 (43%)	7 (15%)	17 (40%)	20 (44%)
CORPUS LUTEUM CYST		2 (4%)		
MULTIPLE CYSTS		2 (4%)		
PAROVARIAN CYST		3 (6%)		
HEMORRHAGIC CYST	1 (3%)	1 (2%)	3 (7%)	2 (4%)
ABSCESS, CHRONIC		1 (2%)		
INFLAMMATION, GRANULOMATOUS				1 (2%)
HYPERPLASIA, GRANULOSA-CELL				1 (2%)
ANGIECTASIS				1 (2%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
FIBROSIS, FOCAL				1 (2%)
#CEREBRUM	(50)	(50)	(50)	(50)
NECROSIS, FOCAL			1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
MINERALIZATION		25 (50%)		
PERIVASCULAR CUFFING		1 (2%)		
NECROSIS, HEMORRHAGIC		1 (2%)		
ATROPHY, PRESSURE				1 (2%)
#BRAIN/THALAMUS	(50)	(50)	(50)	(50)
MINERALIZATION	29 (58%)		17 (34%)	15 (30%)
#HYPOTHALAMUS	(50)	(50)	(50)	(50)
ATROPHY, PRESSURE	1 (2%)		1 (2%)	1 (2%)
*SCIATIC NERVE	(50)	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*CORTEX OF BONE	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY	9 (18%)		23 (46%)	19 (38%)
*FEMUR	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY		18 (36%)		
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)	
NECROSIS, FAT				1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
*PERITONEUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)			
*MEDIASTINAL PLEURA	(50)	(50)	(50)	(50)
NECROSIS, FOCAL				1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)		
NECROSIS, FAT	1 (2%)			
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)		
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF	1			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

METHODS USED IN HEMATOLOGIC ANALYSES

APPENDIX E

A. Packed Cell Volume (PCV, "hematocrit"):

This volume was reported as a percentage of the whole blood volume (Lynchet al., 1969; Miale, 1967) on the Coulter (Coulter Electronics) flat pack accessory.

B. Hemoglobin (HGB):

The red cells in a specimen of blood were hemolyzed and the hemoglobin was converted into either oxy- or cyanomethemoglobin (Lynch et al., 1969; Miale, 1967). The optical density or percent transmittance of a dilute solution was measured and the hemoglobin concentration of the original sample was obtained automatically in grams percent on the Coulter Hemoglobinometer.

C. Erythrocyte Count (RBC):

Whole blood was diluted with an isotonic solution and the number of red blood cells in a known volume was counted automatically on the Coulter Counter, Model FN (Coulter Electronics). RBC is expressed in $10^6/mm^3$ (Lynch et al., 1969; Miale, 1967).

D. Leukocyte Count (WBC):

Whole blood was diluted with an isotonic solution and the number of white cells in a known volume was counted automatically on a Coulter Counter, Model FN. The WBC is expressed in $10^3/mm^3$ (Lynch et al., 1969; Miale, 1967).

E. Differential:

A count of 100 leukocytes was differentiated and reported in percent per type of cell. Slides were stained with May-Grunwald/Giemsa on the Ames automatic slide stainer (Ames Co., 1974).

F. Platelet:

The platelets in a diluted sample of blood were counted in a hemocytometer. Results are reported in $10^3/mm^3$. This direct method of platelet determination was done with the Unopette disposable pipetting system (Becton-Dickinson, Rutherford, NJ).

G. MCV:

MCV was calculated on the Coulter FN flat pack accessory.

H. Reticulocytes:

Reticulocyte counts were performed by making a blood smear from a mixture of equal parts of fresh methylene blue and blood, and then counting from estimated fields containing 1,000 red blood cells.

APPENDIX F

HEMATOLOGY, CLINICAL CHEMISTRY, AND ORGAN WEIGHTS FOR RATS AND MICE IN THE 13-WEEK STUDIES

TABLE F1. HEMATOLOGY DATA FOR RAT ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

DOSE GROUP (mg/kg)	N		HgB (g/dl)	PCV (%)	WBC (10^3/cu mm)	RBC (10^6/cu mm)	MCV (μ^3)	BANDS (%)	SEGS (%)	EOS (%)	BASO (%)	LYMPH (%)	MONO (%)	PLATELETS (per cu mm)	RETIC (%)
MALES															
Vehicle Control	9	$\bar{X}$	16.3	45	7.4	8.89	51	0	21	2	0	78	1	279,200	1.5
		SD	0.4	2	1.1	0.26	2		4	1	0	4	0	77,600	0.9
60	10	$\bar{X}$	16.7	45	7.0	8.99	50	0	19	2	0	80	1	298,800	2.1
		SD	0.5	1	1.0	0.20	1		5	1	0	5	0	50,600	0.6
125	10	$\bar{X}$	16.4	43	7.7	8.80	50	0	20	1	0	79	0	373,800 *(a)*	1.7
		SD	0.5	2	1.7	0.34	1		7	1	0	7	0	61,600	0.9
250	10	$\bar{X}$	15.9	44	6.8	9.10	49 *(b)*	0	23	2	0	76	1	280,500	2.2
		SD	0.5	3	1.6	0.40	1		8	1	0	9	0	45,400	0.8
500	7	$\bar{X}$	15.5 *(a)*	43	7.6	9.03	49 *(b)*	0	29	1	0	71	0	311,400	1.0
		SD	0.7	3	1.5	0.61	1		11	0	0	11	0	87,900	1.0
750	1	$\bar{X}$	14.8 *(a)*	40	7.8	8.13	49	0	24	1	0	75	0	315,000	3.9 *(a)*
FEMALES															
Vehicle Control	10	$\bar{X}$	16.3	45	5.3	8.72	53	0	21	2	0	78	0	411,800	1.6
		SD	0.4	1	0.5	0.26	1		4	2	0	4	0	64,600	0.8
60	10	$\bar{X}$	15.9	42	5.9	7.90 *(a)*	54	0	20	2	1	79	0	349,809	2.8
		SD	0.6	2	0.6	0.23	1		5	1	3	5	0	77,500	1.3
125	10	$\bar{X}$	16.2	49 *(a)*	4.6	8.84	56 *(b)*	0	21	2	1	78	0	407,000	2.2
		SD	0.5	3	0.7	0.31	2		6	1	3	6	0	57,700	1.3
250	10	$\bar{X}$	15.9	48	4.5	8.82	55*(b)*	0	19	2	0	80	1	490,300	1.8
		SD	0.7	2	0.6	0.37	1		4	1	0	3	0	77,300	1.2
500	7	$\bar{X}$	15.8	47	4.6	8.72	53	0	24	1	0	76	0	305,000 *(a)*	3.1
		SD	2.3	6	1.7	1.49	1		11	1	0	11	0	85,000	1.3
750	2	$\bar{X}$	15.2	45	3.3 *(a)*	8.83	51	0	26	2	0	73	0	350,000	2.6
		SD	0.8	3	0.4	0.63	0		1	0	0	1	0	91,900	1.5

(a) P<0.05 relative to vehicle controls.
(b) P<0.01 relative to vehicle controls.

TABLE F2. CLINICAL CHEMISTRY DATA FOR RATS ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose (mg/kg)	N		ALK PHOS. (IU/L)	SGPT (IU/L)	GGTP (IU/L)	BILI. (mg/dl)	CHOLES. (mg/dl)	TRIGLYC. (mg/dl)	BUN (mg/dl)	GLUC. (mg/dl)	TOTAL PROT. (g/dl)	ALBUM. (%)	GLOBULINS alpha (%)	GLOBULINS beta (%)	GLOBULINS gamma (%)
MALES															
Vehicle Control		$\bar{X}$	169	46	0.0	0.27	26	198	22	170	6.4	67.5	10.0	18.7	3.0
	9	SD	11	67	0.0	0.14	8	79	2	11	0.4	1.9	3.3	1.1	0.9
60		$\bar{X}$	154	51	0.0	0.29	39 *(b)*	210	21	176	6.8 *(a)*	69.5	9.9	17.9	2.1 *(a)*
	10	SD	21	28	0.0	0.07	9	46	2	56	0.3	1.4	1.2	1.2	0.6
125		$\bar{X}$	131 *(a)*	102	0.0	0.34	32	198	20	192	6.6	67.3	12.2	17.5	2.3
	10	SD	32	127	0.0	0.21	8	34	2	33	0.4	2.6	2.4	1.6	0.9
250		$\bar{X}$	162	60	0.0	0.31	49 *(b)*	155	19 *(b)*	174	6.8 *(a)*	69.5	10.4	17.5	1.9 *(a)*
	10	SD	32	82	0.0	0.09	13	64	2	22	0.2	2.4	1.8	0.9	0.7
500		$\bar{X}$	171	6	0.0	0.26	43 *(a)*	109 *(a)*	16 *(b)*	158	5.7 *(b)*	67.8	9.7	20.0	1.7 *(b)*
	6	SD	26	9	0.0	0.07	15	32	2	4	0.3	3.0	2.5	1.5	0.5
750		$\bar{X}$	167	217	0.0	0.38	35	58	18	148	6.3	72.5	5.0	19.6	2.2
FEMALES															
Vehicle Control		$\bar{X}$	83	112	0.0	0.30	49	134	21	152	6.6	67.3	11.3	16.5	4.2
	7	SD	12	185	0.0	0.15	10	32	5	26	0.4	2.3	1.9	1.0	0.8
60		$\bar{X}$	72	21	0.0	0.40	75 *(b)*	93 *(b)*	17	169	6.4	66.4	10.6	17.4	5.0
	10	SD	6	4	0.0	0.22	11	22	2	16	0.3	1.4	1.0	0.8	1.3
125		$\bar{X}$	90	25	0.0	0.29	70 *(a)*	90 *(b)*	14 *(b)*	167	6.3	66.7	11.0	17.8	3.7
	10	SD	21	5	0.0	0.09	9	21	2	11	0.1	2.7	2.3	1.3	1.0
250		$\bar{X}$	64	34	0.0	0.21	76 *(b)*	105	17	173	6.8	66.7	11.6	18.2 *(a)*	3.6
	10	SD	24	14	0.0	0.05	12	23	3	20	0.6	2.9	2.7	1.6	0.9
500		$\bar{X}$	141 *(b)*	64	4.0 *(b)*	0.20	71 *(a)*	75 *(b)*	20	165	7.1	66.5	10.7	19.6 *(b)*	2.7 *(a)*
	7	SD	53	31	3.0	0.04	30	27	4	25	0.7	2.3	2.1	0.9	0.9
750		$\bar{X}$	150 *(a)*	206	14.0 *(b)*	0.41	50	91	20	166	7.2	66.7	10.3	19.6 *(b)*	2.3
	2	SD	28	8	6.0	0.22	11	16	3	1	0.9	2.1	1.6	0.7	0.3

(a) $P < 0.05$ relative to vehicle controls.
(b) $P < 0.01$ relative to vehicle controls.

TABLE F3. PORPHYRIN ANALYSIS FOR RATS ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose Group (mg/kg)	Sex	Liver Total Porphyrins *(a)*	Urine Volume *(b)*	Urinary Uroporphyrin *(c)*	Urinary Coproporphyrin *(c)*
Vehicle Control	Male	58 ± 10 (9)	8 ± 2 (9)	1028 ± 282 (9)	343 ± 167 (9)
60	Male	51 ± 8 (10)	-	-	—
125	Male	55 ± 6 (10)	-	-	—
250	Male	62 ± 21 (10)	-	-	—
500	Male	70 ± 33 (6)	11 ± 4 (7)	1509 ± 593 (7)	1649 ± 821 (7) *(e)*
750	Male	94 (1)	19 ± 3 (4) *(e)*	4176 ± 3220 (4) *(e)*	3099 ± 599 (4) *(e)*
Vehicle Control	Female	53 ± 19 (9)	7 ± 1 (10)	588 ± 206 (10)	267± 195 (10)
60	Female	59 ± 12 (9)	-	-	—
125	Female	67 ± 15 (10)	-	-	—
250	Female	51 ± 10 (10)	-	-	—
500	Female	81 ± 21 (7) *(e)*	8 ± 3 (7)	1032 ± 1084 (7)	1631 ± 1048 (7) *(e)*
750	Female	90 ± 34 (2) *(d)*	10 ± 1 (2)	935 ± 202 (2)	594 ± 42 (2)

(a) Nanograms per gram liver; x ± SD (N).
(b) Milliliters per 24 hr; x ± SD (N).
(c) Nanograms per 24 hr; x ± SD (N).
(d) $P<0.05$ relative to vehicle controls.
(e) $P<0.01$ relative to vehicle controls.

TABLE F4. ORGAN WEIGHT ANALYSIS FOR MALE RATS ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose Group (mg/kg)	N		Final Body Weight	Liver[a]	Kidney[b] (right)	Lung[b]	Spleen[b]	Heart[b]	Thymus[c]	Brain[b]	Testis[b] (right)
Vehicle Control	9	Absolute	287 ± 12[d]	11.301 ± 0.975[d]	1.089 ± 0.071	1.513 ± 0.126	0.659 ± 0.050[d]	1.169 ± 0.540[d]	0.343 ± 0.091	1.846 ± 0.081[d]	2.160 ± 0.116[d]
		Organ/Body	-	0.393 ± 0.022[d]	0.379 ± 0.017[d]	0.526 ± 0.038[d]	0.229 ± 0.010[d]	0.407 ± 0.188	1.201 ± 0.362	0.643 ± 0.036[d]	0.752 ± 0.037
60	10	Absolute	282 ± 24	11.243 ± 1.103	1.018 ± 0.089	1.463 ± 0.163	0.557 ± 0.059[e]	0.899 ± 0.079	0.269 ± 0.091	1.821 ± 0.088	2.320 ± 0.184
		Organ/Body	-	0.399 ± 0.025	0.362 ± 0.019	0.519 ± 0.040	0.198 ± 0.016[e]	0.319 ± 0.017	0.944 ± 0.295	0.649 ± 0.048	0.830 ± 0.116
125	10	Absolute	273 ± 17	11.233 ± 1.246	1.046 ± 0.073	1.556 ± 0.133	0.554 ± 0.042[e]	0.945 ± 0.088	0.274 ± 0.072	1.809 ± 0.059	2.163 ± 0.237
		Organ/Body	-	0.412 ± 0.035	0.384 ± 0.027	0.573 ± 0.068	0.203 ± 0.014	0.347 ± 0.037	0.999 ± 0.229	0.666 ± 0.046	0.794 ± 0.081
250	10	Absolute	254 ± 21[e]	12.449 ± 1.595	1.035 ± 0.075	1.433 ± 0.073	0.493 ± 0.072[e]	0.850 ± 0.072	0.282 ± 0.076	1.802 ± 0.050	1.900 ± 0.144
		Organ/Body	-	0.489 ± 0.030[e]	0.408 ± 0.026	0.566 ± 0.034	0.194 ± 0.020[e]	0.336 ± 0.038	1.109 ± 0.290	0.713 ± 0.057	0.750 ± 0.057
500	6	Absolute	249 ± 29[e]	12.053 ± 1.220	1.054 ± 0.057	1.496 ± 0.158	0.489 ± 0.114[e]	0.841 ± 0.157	0.258 ± 0.081	1.759 ± 0.072	1.922 ± 0.217
		Organ/Body	-	0.486 ± 0.040[e]	0.428 ± 0.062[e]	0.612 ± 0.135	0.194 ± 0.027[e]	0.337 ± 0.039	1.030 ± 0.284	0.714 ± 0.080	0.774 ± 0.064
750	1	Absolute	230[e]	12.406	1.040	1.284[e]	0.481[e]	0.808	0.181[e]	1.754	1.863[e]
		Organ/Body	-	0.539[e]	0.452[e]	0.558	0.209	0.351	0.787	0.763[e]	0.810

Values are $\bar{X}$ ± SD
(a) (Organ wt x 10) / body wt
(b) (Organ wt x 100) / body wt
(c) (Organ wt x 1000) / body wt
(d) Statistically significant ($P<0.05$) dose-related trend
(e) Statistically ($P<0.05$) different from control (vehicle)

TABLE F5. ORGAN WEIGHT ANALYSIS FOR FEMALE RATS ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose Group (mg/kg)	N		Final Body Weight	Liver[a]	Kidney[b] (right)	Lung[b]	Spleen[b]	Heart[b]	Thymus[b]	Brain[b]	Ovary[c] (right)	Uterus[b]
Vehicle Control	10	Absolute	160 ± 14	4.944 ± 0.651[d]	0.652 ± 0.057[d]	1.114 ± 0.162[d]	0.420 ± 0.060[d]	0.616 ± 0.045	0.231 ± 0.034	1.755 ± 0.083[d]	0.063 ± 0.026[d]	0.382 ± 0.114[d]
		Organ/Body	-	0.310 ± 0.030[d]	0.409 ± 0.029[d]	0.696 ± 0.068	0.262 ± 0.024[d]	0.387 ± 0.030	0.146 ± 0.031	0.110 ± 0.009	0.39 ± 0.14[d]	0.236 ± 0.058[d]
60	10	Absolute	160 ± 11	5.080 ± 0.273	0.632 ± 0.044	1.128 ± 0.150	0.394+0.032	0.626 ± 0.064	0.258 ± 0.072	1.749 ± 0.071	0.054 ± 0.017	0.435 ± 0.099
		Organ/Body	-	0.317 ± 0.014	0.396 ± 0.033	0.709 ± 0.133	0.246 ± 0.014	0.390 • 0.033	0.160 ± 0.039	0.109 ± 0.006	0.34 ± 0.09	0.270 ± 0.052
125	10	Absolute	164 ± 11	6.077 ± 0.573[e]	0.656 ± 0.045	1.217 ± 0.214	0.407 ± 0.025	0.598 ± 0.036	0.235 ± 0.036	1.741 ± 0.073	0.064 ± 0.017	0.386 ± 0.113
		Organ/Body	-	0.370 ± 0.027[e]	0.400 ± 0.028	0.740 ± 0.120	0.248 ± 0.012	0.364 ± 0.019	0.143 ± 0.019	0.106 ± 0.008	0.39 ± 0.10	0.233 ± 0.058
250	10	Absolute	162 ± 10	6.075 ± 0.523[e]	0.645 ± 0.051	1.067 ± 0.078	0.394 ± 0.034	0.599 ± 0.040	.229 ± 0.046	1.745 ± 0.079	0.056 ± 0.011	0.350 ± 0.065
		Organ/Body	-	0.375 ± 0.039[e]	0.398 ± 0.040	0.658 ± 0.054	0.243 ± 0.020	0.369 ± 0.027	0.140 ± 0.026	0.108 ± 0.006	0.35 ± 0.07	0.215 ± 0.039
500	7	Absolute	149 ± 14	7.244 ± 1.232[e]	0.703 ± 0.055	0.969 ± 0.109	0.364 ± 0.060	0.592 ± 0.067	0.219 ± 0.049	1.622 ± 0.076[e]	0.035 ± 0.007[e]	0.232 ± 0.056[e]
		Organ/Body	-	0.485 ± 0.068[e]	0.474 ± 0.051[e]	0.652 ± 0.064	0.244 ± 0.029	0.397 ± 0.029	0.147 ± 0.032	0.110 ± 0.013	0.24 ± 0.06	0.157 ± 0.043
750	1	Absolute	156	10.154[e]	0.753[e]	0.922	0.327[e]	0.584	0.243	1.691	0.040	0.292
		Organ/Body	-	0.651[e]	0.483[e]	0.591	0.210[e]	0.374	0.156	0.108	0.26	0.187

Values are $\bar{X}$ ± SD
(a) (Organ wt x 10) / body wt
(b) (Organ wt x 100) / body wt
(c) (Organ wt x 1000) / body wt
(d) Statistically significant ($P<0.05$) dose-related trend
(e) Statistically ($P<0.05$) different from control

TABLE F6. HEMATOLOGY DATA FOR MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

DOSE GROUP (mg/kg)	N		HgB (g/dl)	PCV (%)	WBC (10^3/cu mm)	RBC (10^6/cu mm)	MCV (μ^3)	BANDS (%)	SEGS (%)	EOS (%)	BASO (%)	LYMPH (%)	MONO (%)	PLATELETS (per cu mm)	RETIC (%)
MALES															
Vehicle Control	10	$\bar{X}$	15.0	49	8.4	9.94	50	0	17	1	0	83	0	458,600	1.5
		SD	5.3	1	2.0	0.41	1	0	5	1	0	5	0	152,000	0.6
60	10	$\bar{X}$	16.0	49	5.4 *(a)*	10.05	51	0	13	1	0	87	0	458,400	1.6
		SD	0.5	1	1.0	0.27	1	0	3	1	0	4	0	80,100	0.6
125	10	$\bar{X}$	16.5	47 *(a)*	7.7	10.25	48 *(a)*	0	16	1	0	84	0	510,200	1.6
		SD	0.5	1	1.0	0.14	1	0	7	1	0	7	0	199,400	0.9
250	4	$\bar{X}$	15.9	46 *(a)*	6.5	9.57	49	0	21	1	0	78	0	643,800	1.9
		SD	0.2	0	1.3	0.40	2	0	10	2	0	11	0	108,200	1.1
FEMALES															
Vehicle Control	10	$\bar{X}$	16.8	48	6.0	9.87	50	0	19	1	0	80	0	501,600	1.9
		SD	0.3	1	1.0	0.37	1	0	6	1	0	5	0	120,100	0.5
60	10	$\bar{X}$	16.9	48	7.0	10.04	49	0	16	1	0	83	0	482,500	1.6
		SD	0.7	3	1.7	0.76	1	0	5	1	0	5	0	79,500	0.9
125	10	$\bar{X}$	16.6	48	7.1	10.07	48 *(a)*	0	16	2	0	84	0	544,300	1.3
		SD	1.1	3	1.9	0.63	1	0	7	4.2	0	7	0	115,400	0.6
250	6	$\bar{X}$	15.9	47	4.3	9.20	52 *(a)*	0	28	1	0	71	0	666,000	2.2
		SD	0.5	1	0.8	0.40	2	0	13	1	0	13	0	116,300	0.9
500	7	$\bar{X}$	15.2 *(a)*	45	4.9	9.22	49	0	30 *(b)*	3.33	0	70	0	584,500	1.5
		SD	1.6	4	1.3	0.95	1	0	14	1	0	14	0	149,600	0.8

(a) $P < 0.05$ relative to vehicle controls.
(b) $P < 0.01$ relative to vehicle controls.

TABLE F7. CLINICAL CHEMISTRY DATA FOR MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

DOSE GROUP (mg/kg)		ALK PHOS (IU/L)	SGPT (IU/L)	GGTP (IU/L)	BILI (mg/dl)	BUN (mg/dl)
MALES						
Vehicle Control	$\bar{X}$	32	55	0	0.46	21
	SD(N)	7 (7)	25 (7)	0 (5)	0.24 (3)	1 (3)
60	$\bar{X}$	34	37	0	0.39	22
	SD(N)	5 (10)	22 (10)	0 (10)	0.15 (10)	3 (10)
125	$\bar{X}$	29	47	0	0.49	20
	SD(N)	10 (7)	21 (7)	0 (5)	0.62 (4)	2 (4)
250	X	42	35	0	0.25	16
	SD(N)	3 (2)	2 (2)	0 (4)	(1)	(1)
FEMALES						
Vehicle Control	$\bar{X}$	52	58	0	0.37	25
	SD(N)	9 (8)	32 (7)	0 (4)	0.15 (4)	2 (4)
60	$\bar{X}$	49	71	1	0.39	20
	SD(N)	10 (7)	40 (6)	2 (4)	0.20 (3)	3 (3)
125	$\bar{X}$	55	51	0	0.29	22
	SD(N)	15 (6)	38 (5)	0 (3)	0.03 (3)	8 (2)
250	$\bar{X}$	57	78	0	0.44	20
	SD(N)	7 (4)	38 (4)	0 (3)	0.03 (3)	4 (3)
500	$\bar{X}$	56	67	0	0.37	25
	SD(N)	8 (3)	27 (3)	0 (2)	0.21 (2)	6 (2)

No statistically significant differences were observed between control and dosed mice.

TABLE F8. PORPHYRIN ANALYSIS FOR MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

DOSE GROUP (mg/kg)	SEX	LIVER TOTAL PORPHYRIN[a]	URINARY UROPORPHYRIN[b]	URINARY COPROPORPHYRIN[b]
Vehicle Control	Male	100 ± 78 (10)	758 ± 139 (2)	312 ± 266 (2)
60	Male	108 ± 39 (10)	—	—
125	Male	77 ± 17 (10)	603 ± 23 (2)	337 ± 6 (2)
250	Male	100 ± 14 (4)	700 (1)	833 (1)
500	Male	*d*	*d*	*d*
750	Male	*d*	*d*	*d*
Vehicle Control	Female	95 ± 65 (9)	1948 ± 385 (2)	119 ± 7 (2)
60	Female	53 ± 27 (10)	—	—
125	Female	64 ± 19 (10)	—	—
250	Female	87 ± 54 (6)	3060 (1)	2628 (1)[c]
500	Female	62 ± 16 (3)	1587 ± 245 (2)	1675 ± 106 (2)[c]
750	Female	*d*	*d*	*d*

(a) Nanograms per gram liver: $\bar{X}$ ± SD (N)
(b) Nanograms per 24 hr.: $\bar{X}$ ± SD (N)
(c) $P<0.01$ relative to vehicle controls
(d) All animals dead

TABLE F9. ORGAN WEIGHT ANALYSIS FOR MALE MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose Group (mg/kg)	N		Final Body Weight	Liver[a]	Kidney[b] (right)	Lung[b]	Spleen[b]	Heart[b]	Thymus[b]	Brain[a]	Testis[b] (right)
Vehicle Control	10	Absolute	26 ± 1	1.075 ± 0.072[c]	0.227 ± 0.017	0.249 ± 0.036	0.063 ± 0.006	0.164 ± 0.014[c]	0.040 ± 0.010	0.462 ± 0.019	0.197 ± 0.016
		Organ/Body	-	0.415 ± 0.022[c]	0.875 ± 0.058	0.962 ± 0.136	0.245 ± 0.027	0.632 ± 0.048[c]	0.15 ± 0.04	0.179 ± 0.012	0.763 ± 0.072
60	10	Absolute	26 ± 1	1.074 ± 0.074	0.208 ± 0.016	0.200 ± 0.017[d]	0.054 ± 0.007	0.143 ± 0.015[d]	0.038 ± 0.008	0.455 ± 0.063	0.205 ± 0.023
		Organ/Body	-	0.422 ± 0.035	0.815 ± 0.064	0.784 ± 0.052[d]	0.213 ± 0.031	0.561 ± 0.052[d]	0.15 ± 0.03	0.178 ± 0.020	0.802 ± 0.074
125	10	Absolute	25 ± 2	1.181 ± 0.087[d]	0.223 ± 0.017	0.219 ± 0.037	0.060 ± 0.009	0.145 ± 0.010[d]	0.036 ± 0.009	0.438 ± 0.021	0.199 ± 0.016
		Organ/Body	-	0.472 ± 0.030[d]	0.892 ± 0.108	0.872 ± 0.127	0.241 ± 0.040	0.578 ± 0.059	0.15 ± 0.05	0.176 ± 0.020	0.793 ± 0.067
250	4	Absolute	26 ± 2	1.457 ± 0.184[d]	0.239 ± 0.027	0.254 ± 0.020	0.062 ± 0.011	0.139 ± 0.023[d]	0.033 ± 0.016	0.442 ± 0.017	0.178 ± 0.039
		Organ/Body	-	0.559 ± 0.028[d]	0.918 ± 0.052	0.984 ± 0.137	0.235 ± 0.027	0.532 ± 0.052[d]	0.13 ± 0.07	0.171 ± 0.012	0.694 ± 0.188

Values are $\bar{X}$ ± SD

(a) (Organ wt x 10) / body wt

(b) (Organ wt x 100) / body wt

(c) Statistically significant ($P<0.05$) dose-related trend

(d) Statistically ($P<0.05$) different from control

TABLE F10. ORGAN WEIGHT ANALYSIS FOR FEMALE MICE ADMINISTERED CHLOROBENZENE IN THE 13-WEEK STUDY

Dose Group (mg/kg)	N		Final Body Weight	Liver[a]	Kidney[b] (right)	Lung[b]	Spleen[b]	Heart[b]	Thymus[b]	Brain[a]	Ovary[b] (right)	Uterus[b]
Vehicle Control	9	Absolute	21 ± 1	0.959 ± 0.096[d]	0.167 ± 0.020	0.201 ± 0.028	0.071 ± 0.010[d]	0.124 ± 0.011	0.042 ± 0.006	0.461 ± 0.022[d]	0.017 ± 0.003	0.121 ± 0.029
		Organ/Body	-	0.453 ± 0.018[d]	0.789 ± 0.065[d]	0.952 ± 0.114	0.336 ± 0.043	0.586 ± 0.022	0.20 ± 0.03	0.219 ± 0.010	0.078 ± 0.015	0.575 ± 0.133
60	9	Absolute	22 ± 2	1.056 ± 0.140	0.162 ± 0.017	0.225 ± 0.060	0.076 ± 0.010	0.119 ± 0.009	0.044 ± 0.011	0.446 ± 0.018	0.019 ± 0.006	0.116 ± 0.024
		Organ/Body	-	0.473 ± 0.035	0.733 ± 0.035	1.038 ± 0.261	0.344 ± 0.047	0.540 + 0.036	0.20 ± 0.05	0.203 ± 0.008	0.088 ± 0.030	0.509 ± 0.103
125	10	Absolute	22 ± 1	1.071 ± 0.079	0.165 ± 0.013	0.222 ± 0.046	0.066 ± 0.006	0.119 ± 0.016	0.042 ± 0.005	0.449 ± 0.019	0.022 ± 0.005	0.108 ± 0.033
		Organ/Body	-	0.496 ± 0.025	0.767 ± 0.049	1.025 ± 0.161	0.305 ± 0.033	0.554 ± 0.080	0.20 ± 0.03	0.209 ± 0.012	0.103 ± 0.025	0.500 ± 0.150
250	6	Absolute	21 ± 1	1.227 ± 0.065[e]	0.177 ± 0.018	0.204 ± 0.039	0.084 ± 0.019	0.130 ± 0.006	0.117 ± 0.168	0.445 ± 0.023	0.021 ± 0.009	0.104 ± 0.018
		Organ/Body	-	0.576 ± 0.015[e]	0.831 ± 0.060	0.939 ± 0.132	0.394 ± 0.079	0.609 ± 0.049	0.55 ± 0.80	0.209 ± 0.010	0.099 ± 0.038	0.490 ± 0.082
500	3	Absolute	20 ± 3	1.617 ± 0.179[e]	0.181 ± 0.018	0.213 ± 0.031	0.068 ± 0.016[f]	0.125 ± 0.021	0.051 ± 0.019	0.415 ± 0.021[e]	0.015 ± 0.005	0.091 ± 0.043
		Organ/Body	-	0.807 ± 0.147[e]	0.908 ± 0.190[e]	1.083 ± 0.336	0.310 ± 0.094[f]	0.644 ± 0.054	0.23 ± 0.07	0.207 ± 0.030	0.076 ± 0.025	0.434 ± 0.148

Values are $\bar{X}$ ± SD

(a) (Organ wt x 10)/body wt

(b) (Organ wt x 100)/body wt

(c) (Organ wt x 1000)/body wt

(d) Statistically significant ($P<0.05$) dose-related trend

(e) Statistically ($P<0.05$) different from control

(f) N=2 for the spleen; a single animal was recorded as having a splenic weight of 10x normal, despite a lack of recorded gross or microscopic abnormality. The weight, therefore, was considered to be wrongly recorded and was censored from analysis.

APPENDIX G

MEAN BODY WEIGHTS OF RATS AND MICE ADMINISTERED CHLOROBENZENE BY GAVAGE FOR TWO YEARS

TABLE G1. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF RATS ADMINISTERED CHLOROBENZENE BY GAVAGE FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	205	50	208	101.5	50	205	100.0	50
1	221	50	224	101.4	50	221	100.0	50
2	242	50	241	99.6	50	238	98.3	50
3	258	50	256	99.2	50	253	98.1	50
4	274	50	268	97.8	50	266	97.1	50
5	286	50	282	98.6	50	278	97.2	50
6	300	50	295	98.3	50	291	97.0	49
7	309	50	307	99.4	50	301	97.4	49
8	320	50	314	98.1	50	312	97.5	49
9	328	50	323	98.5	50	317	96.6	49
10	334	50	331	99.1	50	324	97.0	49
11	336	50	330	98.2	50	334	99.4	49
12	346	50	343	99.1	50	340	98.3	49
13	353	50	353	100.0	50	347	98.3	49
17	373	50	368	98.7	50	364	97.6	49
22	396	50	391	98.7	50	382	96.5	49
27	411	50	407	99.0	48	400	97.3	48
31	419	50	415	99.0	48	407	97.1	47
35	430	50	426	99.1	48	417	97.0	47
39	439	50	437	99.5	48	429	97.7	45
45	451	50	447	99.1	47	441	97.8	45
49	462	50	459	99.4	47	457	98.9	45
54	469	50	469	100.0	47	463	98.7	44
58	470	50	467	99.4	47	459	97.7	44
62	475	50	474	99.8	47	470	98.9	44
67	478	49	473	99.0	46	465	97.3	44
71	487	49	483	99.2	46	476	97.7	42
75	485	49	482	99.4	46	477	98.4	41
79	483	49	475	98.3	45	475	98.3	40
83	478	49	476	99.6	42	479	100.2	38
87	475	48	472	99.4	42	475	100.0	34
91	468	45	463	98.9	39	462	98.7	30
95	458	43	462	100.9	38	461	100.7	28
100	451	41	456	101.1	35	454	100.7	27
FEMALE								
0	135	50	130	96.3	50	133	98.5	50
1	149	50	150	100.7	50	150	100.7	50
2	157	50	155	98.7	50	157	100.0	50
3	161	50	163	101.2	50	161	100.0	50
4	170	50	169	99.4	50	166	97.6	50
5	173	50	173	100.0	50	173	100.0	50
6	178	50	177	99.4	50	176	98.9	50
7	180	50	179	99.4	50	179	99.4	48
8	187	50	185	98.9	50	184	98.4	48
9	189	50	188	99.5	50	188	99.5	48
10	191	50	192	100.5	50	190	99.5	48
11	194	50	196	101.0	49	195	100.5	47
12	197	50	198	100.5	49	196	99.5	46
13	198	50	200	101.0	49	200	101.0	46
17	206	50	207	100.5	49	204	99.0	46
22	214	50	218	101.9	49	218	101.9	46
27	217	49	220	101.4	46	220	101.4	43
31	220	42	223	101.4	41	226	102.7	41
35	224	42	229	102.2	41	231	103.1	41
39	231	42	239	103.5	40	239	103.5	41
45	236	40	245	103.8	40	247	104.7	41
49	246	40	253	102.8	40	256	104.1	41
54	252	40	259	102.8	40	264	104.8	41
58	251	40	263	104.8	40	263	104.8	41
62	258	40	273	105.8	40	274	106.2	41
67	265	39	279	105.3	40	281	106.0	41
71	272	39	292	107.4	40	294	108.1	41
75	276	39	300	108.7	39	302	109.4	40
79	274	38	300	109.5	36	300	109.5	40
83	280	36	297	106.1	36	299	106.8	39
87	281	34	302	107.5	36	304	108.2	36
91	289	33	308	106.6	34	304	105.2	35
95	289	33	305	105.5	32	309	106.9	33
100	291	31	312	107.2	32	316	108.6	32

TABLE G2. MEAN BODY WEIGHTS (RELATIVE TO CONTROLS) OF MICE ADMINISTERED CHLOROBENZENE BY GAVAGE FOR TWO YEARS

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	23	50	24	104.3	50	23	100.0	50
1	25	50	26	104.0	49	25	100.0	50
2	27	50	27	100.0	49	25	92.6	50
3	30	50	29	96.7	49	28	93.3	50
4	31	50	31	100.0	49	29	93.5	50
5	34	50	33	97.1	49	31	91.2	50
6	30	50	30	100.0	49	28	93.3	50
7	30	50	30	100.0	49	30	100.0	50
8	31	50	31	100.0	49	31	100.0	50
9	32	50	31	96.9	49	31	96.9	50
10	33	50	34	103.0	49	32	97.0	50
11	33	50	34	103.0	49	33	100.0	50
12	34	50	35	102.9	49	34	100.0	50
13	34	50	35	102.9	49	34	100.0	50
17	35	50	36	102.9	49	35	100.0	50
22	36	50	38	105.6	49	37	102.8	50
27	37	50	38	102.7	49	39	105.4	48
31	40	50	39	97.5	48	40	100.0	48
37	39	50	39	100.0	46	40	102.6	47
39	40	50	40	100.0	46	41	102.5	47
43	40	50	40	100.0	46	41	102.5	47
49	41	50	41	100.0	45	41	100.0	47
53	41	50	42	102.4	44	42	102.4	47
58	42	50	42	100.0	44	42	100.0	47
62	43	49	42	97.7	44	43	100.0	47
67	42	49	43	102.4	44	43	102.4	45
72	42	49	41	97.6	44	42	100.0	45
76	43	48	42	97.7	43	43	100.0	43
80	43	47	42	97.7	42	43	100.0	43
84	42	47	41	97.6	41	43	102.4	43
88	42	45	41	97.6	39	42	100.0	41
92	41	44	40	97.6	37	41	100.0	38
96	39	42	39	100.0	35	40	102.6	35
100	39	39	39	100.0	33	39	100.0	32
FEMALE								
0	17	50	16	94.1	50	17	100.0	50
1	20	50	19	95.0	50	20	100.0	50
2	21	50	21	100.0	50	21	100.0	50
3	21	50	22	104.8	50	22	104.8	50
4	22	50	23	104.5	50	23	104.5	50
5	23	50	24	104.3	50	23	100.0	50
6	23	50	24	104.3	50	23	100.0	50
7	22	50	24	109.1	50	23	104.5	50
8	23	50	24	104.3	50	25	108.7	50
9	25	50	24	96.0	50	26	104.0	50
10	26	50	26	100.0	50	26	100.0	50
11	26	50	26	100.0	50	26	100.0	50
12	26	50	27	103.8	50	27	103.8	50
13	26	50	27	103.8	50	27	103.8	50
17	27	50	28	103.7	50	27	100.0	50
22	29	50	29	100.0	50	29	100.0	50
27	31	50	31	100.0	50	30	96.8	49
31	30	50	31	103.3	50	31	103.3	49
37	31	50	32	103.2	50	32	103.2	49
39	32	50	33	103.1	50	33	103.1	49
43	32	50	32	100.0	50	33	103.1	49
49	33	50	34	103.0	50	33	100.0	49
53	34	50	34	100.0	49	34	100.0	48
58	35	50	36	102.9	49	35	100.0	48
62	36	50	36	100.0	48	36	100.0	48
67	35	50	36	102.9	48	36	102.9	48
72	36	49	36	100.0	47	37	102.8	47
76	38	49	38	100.0	47	38	100.0	47
80	38	49	38	100.0	47	38	100.0	47
84	37	49	38	102.7	47	38	102.7	46
88	37	49	38	102.7	47	38	102.7	46
92	37	49	37	100.0	47	37	100.0	46
96	37	48	36	97.3	43	37	100.0	43
100	36	47	35	97.2	43	35*	97.2	42
105	0	0	0	-	0	0	-	0

APPENDIX H

HISTORICAL INCIDENCE OF TUMORS IN CORN OIL CONTROL F344/N RATS

TABLE H1. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Neoplastic Nodule	Carcinoma	Neoplastic Nodule or Carcinoma
Battelle	2/100 (2%) *(b)*	2/100 (2%)	4/100 (4%)
Gulf South	7/291 (2%)	3/291 (1%)	10/291 (3%)
Litton	7/50 (14%)	0/50 (0%)	7/50 (14%)
Mason	1/50 (2%)	2/50 (4%)	3/50 (6%)
Papanicolaou	0/49 (0%)	0/49 (0%)	0/49 (0%)
Southern	4/249 (2%)	0/249 (0%)	4/249 (2%)
Total	21/789 (2.7%)	7/789 (0.9%)	28/789 (3.5%)
SD *(c)*	3.81%	1.63%	4.07%
Range			
High	7/50	2/50	7/50
Low	0/50	0/50	0/50

(a) Data as of January 5, 1983 for studies of at least 104 weeks in the new NTP historical control data base (from Technical Reports 193 forward).
(b) Includes this study; incidence was 0/50 (0%) in the other study from Battelle.
(c) Standard deviation. Range and SD are presented for groups of 35 or more animals.

APPENDIX I

ANALYSIS OF PRIMARY TUMORS IN RATS AND MICE

TABLE I1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Fibroma				
Tumor Rates				
Overall *(a)*	4/50 (8%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted *(b)*	11.8%	12.3%	6.1%	6.4%
Terminal *(c)*	4/34 (12%)	4/39 (10%)	1/32 (3%)	1/26 (4%)
Statistical Tests *(d)*				
Life Table		P=0.286N	P=0.302N	P=0.396N
Incidental Tumor Test		P=0.209N	P=0.207N	P=0.311N
Cochran-Armitage Trend Test		P=0.146N		
Fisher Exact Test			P=0.218N	P=0.218N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Tumor Rates				
Overall *(a)*	4/50 (8%)	7/50 (14%)	2/50 (4%)	3/50 (6%)
Adjusted *(b)*	11.8%	16.7%	6.1%	9.7%
Terminal *(c)*	4/34 (12%)	5/39 (13%)	1/32 (3%)	1/26 (4%)
Statistical Tests *(d)*				
Life Table		P=0.238N	P=0.137N	P=0.360N
Incidental Tumor Test		P=0.134N	P=0.088N	P=0.219N
Cochran-Armitage Trend Test		P=0.099N		
Fisher Exact Test			P=0.080N	P=0.159N
Subcutaneous Tissue: Sarcoma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted *(b)*	0.0%	6.7%	0.0%	3.6%
Terminal *(c)*	0/34 (0%)	1/39 (3%)	0/32 (0%)	0/26 (0%)
Statistical Tests *(d)*				
Life Table		P=0.269N	P=0.152N	P=0.453N
Incidental Tumor Test		P=0.138N	P=0.151N	P=0.250N
Cochran-Armitage Trend Test		P=0.176N		
Fisher Exact Test			P=0.121N	P=0.309N
Hematopoietic System: Mononuclear Cell Leukemia				
Tumor Rates				
Overall *(a)*	12/50 (24%)	5/50 (10%)	9/50 (18%)	3/50 (6%)
Adjusted *(b)*	32.2%	11.5%	24.3%	9.3%
Terminal *(c)*	9/34 (26%)	2/39 (5%)	5/32 (16%)	1/26 (4%)
Statistical Tests *(d)*				
Life Table		P=0.541	P=0.122	P=0.568N
Incidental Tumor Test		P=0.348N	P=0.224	P=0.331N
Cochran-Armitage Trend Test		P=0.318N		
Fisher Exact Test			P=0.194	P=0.357N
Hematopoietic System: All Leukemia				
Tumor Rates				
Overall *(a)*	19/50 (38%)	8/50 (16%)	11/50 (22%)	4/50 (8%)
Adjusted *(b)*	44.5%	17.8%	27.8%	12.9%
Terminal *(c)*	11/34 (32%)	3/39 (8%)	5/32 (16%)	2/26 (8%)
Statistical Tests *(d)*				
Life Table		P=0.424N	P=0.195	P=0.404N
Incidental Tumor Test		P=0.152N	P=0.327	P=0.167N
Cochran-Armitage Trend Test		P=0.166N		
Fisher Exact Test			P=0.306	P=0.178N

TABLE H. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Liver: Neoplastic Nodule				
Tumor Rates				
Overall *(a)*	4/50 (8%)	2/50 (4%)	4/49 (8%)	8/49 (16%)
Adjusted *(b)*	10.4%	4.5%	12.5%	29.3%
Terminal *(c)*	2/34 (6%)	0/39 (0%)	4/32 (13%)	7/26 (27%)
Statistical Tests *(d)*				
Life Table		P=0.005	P=0.255	P=0.010
Incidental Tumor Test		P=0.011	P=0.290	P=0.021
Cochran-Armitage Trend Test		P=0.027		
Fisher Exact Test			P=0.329	P=0.043
Liver: Neoplastic Nodule or Carcinoma				
Tumor Rates				
Overall *(a)*	4/50 (8%)	4/50 (8%)	4/49 (8%)	8/49 (16%)
Adjusted *(b)*	10.4%	9.4%	12.5%	29.3%
Terminal *(c)*	2/34 (6%)	2/39 (5%)	4/32 (13%)	7/26 (27%)
Statistical Tests *(d)*				
Life Table		P=0.033	P=0.532	P=0.048
Incidental Tumor Test		P=0.054	P=0.570	P=0.083
Cochran-Armitage Trend Test		P=0.121		
Fisher Exact Test			P=0.631	P=0.168
Pituitary: Adenoma				
Tumor Rates				
Overall *(a)*	20/49 (41%)	10/50 (20%)	9/42 (21%)	3/47 (6%)
Adjusted *(b)*	47.5%	24.2%	27.4%	10.6%
Terminal *(c)*	12/33 (36%)	8/39 (21%)	7/30 (23%)	2/25 (8%)
Statistical Tests *(d)*				
Life Table		P=0.172N	P=0.477	P=0.162N
Incidental Tumor Test		P=0.109N	P=0.532	P=0.101N
Cochran-Armitage Trend Test		P=0.047N		
Fisher Exact Test			P=0.534	P=0.046N
Pituitary: Adenoma, Adenocarcinoma or Carcinoma				
Tumor Rates				
Overall *(a)*	20/49 (41%)	12/50 (24%)	9/42 (21%)	3/47 (6%)
Adjusted *(b)*	**47.5%**	28.3%	27.4%	10.6%
Terminal *(c)*	**12/33 (36%)**	9/39 (23%)	7/30 (23%)	2/25 (8%)
Statistical Tests *(d)*				
Life Table		P=0.084N	P=0.541N	P=0.086N
Incidental Tumor Test		P=0.044N	P=0.462N	P=0.044N
Cochran-Armitage Trend Test		P=0.016N		
Fisher Exact Test			P=0.484N	P=0.015N
Adrenal: Pheochromocytoma				
Tumor Rates				
Overall *(a)*	10/49 (20%)	11/49 (22%)	7/49 (14%)	5/49 (10%)
Adjusted *(b)*	27.2%	25.7%	20.8%	19.2%
Terminal *(c)*	8/34 (24%)	7/38 (18%)	6/32 (19%)	5/26 (19%)
Statistical Tests *(d)*				
Life Table		P=0.231N	P=0.351N	P=0.290N
Incidental Tumor Test		P=0.163N	P=0.231N	P=0.204N
Cochran-Armitage Trend Test		P=0.063N		
Fisher Exact Test			P=0.217N	P=0.085N

TABLE I1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Thyroid: Follicular Cell Adenoma, Adenocarcinoma or Carcinoma				
Tumor Rates				
Overall *(a)*	1/49 (2%)	2/50 (4%)	3/49 (6%)	1/43 (2%)
Adjusted *(b)*	2.9%	5.1%	9.4%	3.8%
Terminal *(c)*	1/34 (3%)	2/39 (5%)	3/32 (9%)	1/26 (4%)
Statistical Tests *(d)*				
Life Table		P=0.563N	P=0.410	P=0.640N
Incidental Tumor Test		P=0.563N	P=0.410	P=0.640N
Cochran-Armitage Trend Test		P=0.458N		
Fisher Exact Test			P=0.490	P=0.557N
Thyroid: C-Cell Carcinoma				
Tumor Rates				
Overall *(a)*	6/49 (12%)	6/50 (12%)	5/49 (10%)	3/43 (7%)
Adjusted *(b)*	16.0%	14.9%	15.6%	11.5%
Terminal *(c)*	3/34 (9%)	5/39 (13%)	5/32 (16%)	3/26 (12%)
Statistical Tests *(d)*				
Life Table		P=0.414N	P=0.615	P=0.472N
Incidental Tumor Test		P=0.404N	P=0.591N	P=0.463N
Cochran-Armitage Trend Test		P=0.264N		
Fisher Exact Test			P=0.514N	P=0.324N
Testis: Interstitial Cell Tumor				
Tumor Rates				
Overall *(a)*	47/50 (94%)	44/50 (88%)	43/49 (88%)	43/50 (86%)
Adjusted *(b)*	100%	93.6%	97.7%	100.0%
Terminal *(c)*	34/34 (100%)	36/39 (92%)	31/32 (97%)	26/26 (100%)
Statistical Tests *(d)*				
Life Table		P=0.002	P=0.110	P=0.003
Incidental Tumor Test		P=0.022	P=0.288	P=0.035
Cochran-Armitage Trend Test		P=0.440N		
Fisher Exact Test			P=0.606N	P=0.500N
Testis: Interstitial Cell Tumor or Interstitial Cell Tumor, Malignant				
Tumor Rates				
Overall *(a)*	47/50 (94%)	45/50 (90%)	43/49 (88%)	43/50 (86%)
Adjusted *(b)*	100%	93.7%	97.7%	100.0%
Terminal *(c)*	34/34 (100%)	36/39 (92%)	31/32 (97%)	26/26 (100%)
Statistical Tests *(d)*				
Life Table		P=0.004	P=0.155	P=0.006
Incidental Tumor Test		P=0.054	P=0.390	P=0.080
Cochran-Armitage Trend Test		P=0.323N		
Fisher Exact Test			P=0.486N	P=0.380N
Tunica Vaginalis: Mesothelioma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted *(b)*	0.0%	7.7%	3.1%	3.1%
Terminal *(c)*	0/34 (0%)	3/39 (8%)	1/32 (3%)	0/26 (0%)
Statistical Tests *(d)*				
Life Table		P=0.316N	P=0.378N	P=0.453N
Incidental Tumor Test		P=0.261N	P=0.378N	P=0.368N
Cochran-Armitage Trend Test		P=0.202N		
Fisher Exact Test			P=0.309N	P=0.309N

TABLE II. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
All Sites: Mesothelioma				
Tumor Rates				
Overall *(a)*	1/50 (2%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	2.0%	7.7%	3.1%	9.3%
Terminal *(c)*	0/34 (0%)	3/39 (8%)	1/32 (3%)	0/26 (0%)
Statistical Tests *(d)*				
Life Table		P=0.432	P=0.378N	P=0.484
Incidental Tumor Test		P=0.565	P=0.378N	P=0.649
Cochran-Armitage Trend Test		P=0.594		
Fisher Exact Test			P=0.309N	P=0.661

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(c) Observed tumor incidence at terminal kill.

(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. 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 I2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia				
Tumor Rates				
Overall *(a)*	3/49 (6%)	5/50 (10%)	8/50 (16%)	11/50 (22%)
Adjusted *(b)*	7.5%	15.2%	22.8%	30.0%
Terminal *(c)*	2/36 (6%)	3/29 (10%)	3/30 (10%)	6/31 (19%)
Statistical Tests *(d)*				
Life Table		P=0.093	P=0.304	P=0.116
Incidental Tumor Test		P=0.041	P=0.257	P=0.055
Cochran-Armitage Trend Test		P=0.067		
Fisher Exact Test			P=0.277	P=0.086
Hematopoietic System: Undifferentiated Leukemia				
Tumor Rates				
Overall *(a)*	0/49 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted *(b)*	0.0%	9.6%	2.7%	0.0%
Terminal *(c)*	0/36 (0%)	2/29 (7%)	0/30 (0%)	0/31 (0%)
Statistical Tests *(d)*				
Life Table		P=0.058N	P=0.304N	P=0.112N
Incidental Tumor Test		P=0.061N	P=0.312N	P=0.105N
Cochran-Armitage Trend Test		P=0.060N		
Fisher Exact Test			P=0.309N	P=0.121N
Hematopoietic System: All Leukemia				
Tumor Rates				
Overall *(a)*	9/49 (18%)	8/50 (16%)	10/50 (20%)	11/50 (22%)
Adjusted *(b)*	22.3%	24.1%	26.8%	30.0%
Terminal *(c)*	6/36 (17%)	5/29 (17%)	3/30 (10%)	6/31 (19%)
Statistical Tests *(d)*				
Life Table		P=0.317	P=0.426	P=0.359
Incidental Tumor Test		P=0.196	P=0.418	P=0.258
Cochran-Armitage Trend Test		P=0.263		
Fisher Exact Test			P=0.398	P=0.306
Hematopoietic System: Lymphoma or Leukemia				
Tumor Rates				
Overall *(a)*	9/49 (18%)	9/50 (18%)	10/50 (20%)	11/50 (22%)
Adjusted *(b)*	22.3%	27.2%	26.8%	30.0%
Terminal *(c)*	6/36 (17%)	6/29 (21%)	3/30 (10%)	6/31 (19%)
Statistical *(d)*				
Life Table		P=0.408	P=0.523	P=0.456
Incidental Tumor Test		P=0.287	P=0.533	P=0.357
Cochran-Armitage Trend Test		P=0.354		
Fisher Exact Test			P=0.500	P=0.402
Pituitary: Adenoma				
Tumor Rates				
Overall *(a)*	27/48 (56%)	23/46 (50%)	18/46 (39%)	13/43 (30%)
Adjusted *(b)*	63.6%	67.0%	56.1%	41.6%
Terminal *(c)*	20/35 (57%)	16/27 (59%)	15/29 (52%)	9/26 (35%)
Statistical Tests *(d)*				
Life Table		P=0.027N	P=0.146N	P=0.039N
Incidental Tumor Test		P=0.016N	P=0.252N	P=0.021N
Cochran-Armitage Trend Test		P=0.036N		
Fisher Exact Test			P=0.201N	P=0.046N

TABLE I2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Pituitary : Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	28/48 (58%)	23/46 (50%)	19/46 (41%) *(e)*	13/43 (30%)
Adjusted *(b)*	64.5%	67.0%	59.2%	41.6%
Terminal *(c)*	20/35 (57%)	16/27 (59%)	16/29 (55%)	9/26 (35%)
Statistical Tests *(d)*				
Life Table		P=0.027N	P=0.195N	P=0.039N
Incidental Tumor Test		P=0.016N	P=0.333N	P=0.021N
Cochran-Armitage Trend Test		P=0.037N		
Fisher Exact Test			P=0.265N	P=0.046N
Adrenal: Pheochromocytoma				
Tumor Rates				
Overall *(a)*	3/49 (6%)	1/49 (2%)	4/49 (8%)	2/49 (4%)
Adjusted *(b)*	8.3%	3.6%	13.1%	6.5%
Terminal *(c)*	8/36 (8%)	1/28 (4%)	3/29 (10%)	2/31 (6%)
Statistical Tests *(d)*				
Life Table		P=0.444	P=0.189	P=0.536
Incidental Tumor Test		P=0.427	P=0.189	P=0.536
Cochran-Armitage Trend Test		P=0.406		
Fisher Exact Test			P=0.181	P=0.500
Thyroid: Follicular Cell Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	0/49 (0%)	0/49 (0%)	2/49 (4%)	3/49 (6%)
Adjusted *(b)*	0.0%	0.0%	6.5%	9.7%
Terminal *(c)*	0/36 (0%)	0/29 (0%)	1/30 (3%)	3/31 (10%)
Statistical Tests *(d)*				
Life Table		P=0.091	P=0.247	P=0.132
Incidental Tumor Test		P=0.082	P=0.212	P=0.132
Cochran-Armitage Trend Test		P=0.082		
Fisher Exact Test			P=0.247	P=0.121
Thyroid: C-Cell Carcinoma				
Tumor Rates				
Overall *(a)*	3/49 (6%)	4/49 (8%)	1/49 (2%)	1/49 (2%)
Adjusted *(b)*	8.3%	13.8%	3.3%	3.2%
Terminal *(c)*	3/36 (8%)	4/29 (14%)	1/30 (3%)	1/31 (3%)
Statistical Tests *(d)*				
Life Table		P=0.088N	P=0.167N	P=0.158N
Incidental Tumor Test		P=0.088N	P=0.167N	P=0.158N
Cochran-Armitage Trend Test		P=0.101N		
Fisher Exact Test			P=0.181N	P=0.181N
Mammary Gland: Fibroadenoma				
Tumor Rates				
Overall *(a)*	7/49 (14%) *(f)*	7/50 (14%)	5/50 (10%)	7/50 (14%) *(g)*
Adjusted *(b)*	17.6%	23.1%	14.9%	21.7%
Terminal *(c)*	5/36 (14%)	6/29 (21%)	3/30 (10%)	6/31 (19%)
Statistical Tests *(d)*				
Life Table		P=0.517N	P=0.364N	P=0.570N
Incidental Tumor Test		P=0.550N	P=0.372N	P=0.604N
Cochran-Armitage Trend Test		P=0.560		
Fisher Exact Test			P=0.380N	P=0.613

TABLE I2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Mammary Gland: All Adenoma				
Tumor Rates				
Overall *(a)*	9/49 (18%) *(f)*	9/50 (18%)	7/50 (14%)	7/50 (14%) *(g)*
Adjusted *(b)*	21.2%	27.9%	21.2%	21.7%
Terminal *(c)*	5/36 (14%)	7/29 (24%)	5/30 (17%)	6/31 (19%)
Statistical Tests *(d)*				
Life Table		P=0.301N	P=0.378N	P=0.354N
Incidental Tumor Test		P=0.325N	P=0.381N	P=0.381N
Cochran-Armitage Trend Test		P=0.339N		
Fisher Exact Test			P=0.393N	P=0.393N
Uterus: Endometrial Stromal Polyp				
Tumor Rates				
Overall *(a)*	9/49 (18%)	16/50 (32%)	4/49 (8%)	10/50 (20%)
Adjusted *(b)*	23.2%	51.3%	13.3%	29.3%
Terminal *(c)*	7/36 (19%)	14/29 (48%)	4/30 (13%)	8/31 (26%)
Statistical Tests *(d)*				
Life Table		P=0.060N	P=0.002N	P=0.090N
Incidental Tumor Test		P=0.059N	P=0.002N	P=0.088N
Cochran-Armitage Trend Test		P=0.085N		
Fisher Exact Test			P=0.003N	P=0.127N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. 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) One animal had both a carcinoma and an adenocarcinoma.
(f) One animal also had a papillary adenocarcinoma.
(g) One animal also had a fibroadenocarcinoma.

TABLE I3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Untreated Control	Vehicle Control	30 mg/kg	60 mg/kg
Skin or Subcutaneous Tissue: Sarcoma, NOS				
Tumor Rates				
Overall *(a)*	1/50 (2%)	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted *(b)*	2.3%	4.5%	7.1%	15.5%
Terminal *(c)*	0/35 (0%)	1/39 (3%)	2/28 (7%)	1/29 (3%)
Statistical Tests *(d)*				
Life Table		P=0.055	P=0.590	P=0.095
Incidental Tumor Test		P=0.126	P=0.602	P=0.260
Cochran-Armitage Trend Test		P=0.080		
Fisher Exact Test			P=0.691	P=0.134
Skin or Subcutaneous Tissue: Fibrosarcoma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted *(b)*	0.0%	0.0%	2.5%	3.4%
Terminal *(c)*	0/35 (0%)	0/39 (0%)	0/28 (0%)	1/29 (3%)
Statistical Tests *(d)*				
Life Table		P=0.295	P=0.472	P=0.441
Incidental Tumor Test		P=0.322	P=0.545	P=0.441
Cochran-Armitage Trend Test		P=0.331		
Fisher Exact Test			P=0.500	P=0.500
Skin or Subcutaneous Tissue: Neurofibrosarcoma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted *(b)*	0.0%	6.9%	3.6%	6.9%
Terminal *(c)*	0/35 (0)%	0/39 (0%)	1/28 (4%)	2/29 (7%)
Statistical Tests *(d)*				
Life Table		P=0.500	P=0.388N	P=0.606
Incidental Tumor Test		P=0.355N	P=0.176N	P=0.392N
Cochran-Armitage Trend Test		P=0.399N		
Fisher Exact Test			P=0.309N	P=0.500N
Skin or Subcutaneous Tissue: Sarcoma, All Types				
Tumor Rates				
Overall *(a)*	1/50 (2%)	5/50 (10%)	4/50 (8%)	9/50 (18%)
Adjusted *(b)*	2.3%	11.1%	12.9%	24.5%
Terminal *(c)*	0/35 (0%)	1/39 (3%)	3/28 (11%)	4/29 (14%)
Statistical Tests *(d)*				
Life Table		P=0.082	P=0.625	P=0.116
Incidental Tumor Test		P=0.204	P=0.456N	P=0.350
Cochran-Armitage Trend Test		P=0.141		
Fisher Exact Test			P=0.500N	P=0.194
Lung: Alveolar/Bronchiolar Adenoma				
Tumor Rates				
Overall *(a)*	5/50 (10%)	4/50 (8%)	3/49 (6%)	6/49 (12%)
Adjusted *(b)*	14.3%	9.8%	11.1%	19.2%
Terminal *(c)*	5/35 (14%)	3/39 (8%)	3/27 (11%)	5/29 (17%)
Statistical Tests *(d)*				
Life Table		P=0.170	P=0.626	P=0.221
Incidental Tumor Test		P=0.199	P=0.626N	P=0.276
Cochran-Armitage Trend Test		P=0.286		
Fisher Exact Test			P=0.511N	P=0.357

TABLE I3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Untreated Control	Vehicle Control	30 mg/kg	60 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma				
Tumor Rates				
Overall *(a)*	1/50 (2%)	2/50 (4%)	1/49 (2%)	4/49 (8%)
Adjusted *(b)*	2.9%	4.7%	3.7%	11.6%
Terminal *(c)*	1/35 (3%)	1/39 (3%)	1/27 (4%)	2/29 (7%)
Statistical Tests *(d)*				
Life Table		P=0.173	P=0.607N	P=0.248
Incidental Tumor Test		P=0.207	P=0.559N	P=0.311
Cochran-Armitage Trend Test		P=0.232		
Fisher Exact Test			P=0.508N	P=0.329
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	5/50 (10%)	6/50 (12%)	4/49 (8%)	10/49 (20%)
Adjusted *(b)*	14.3%	14.3%	14.8%	29.6%
Terminal *(c)*	5/35 (14%)	4/39 (10%)	4/27 (15%)	7/29 (24%)
Statistical Tests *(d)*				
Life Table		P=0.066	P=0.587N	P=0.094
Incidental Tumor Test		P=0.087	P=0.508N	P=0.136
Cochran-Armitage Trend Test		P=0.143		
Fisher Exact Test			P=0.383N	P=0.194
Hematopoietic System: Malignant Lymphoma, Histiocytic Type				
Tumor Rates				
Overall *(a)*	0/50 (0%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted *(b)*	0.0%	4.2%	12.9%	7.5%
Terminal *(c)*	0/35 (0%)	0/39 (0%)	2/28 (7%)	0/29 (0%)
Statistical Tests *(d)*				
Life Table		P=0.336	P=0.245	P=0.447
Incidental Tumor Test		P=0.577N	P=0.392	P=0.626N
Cochran-Armitage Trend Test		P=0.417		
Fisher Exact Test			P=0.339	P=0.500
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type				
Tumor Rates				
Overall *(a)*	1/50 (2%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted *(b)*	2.9%	5.1%	10.0%	9.2%
Terminal *(c)*	1/35 (3%)	2/39 (5%)	2/28 (7%)	1/29 (3%)
Statistical Tests *(d)*				
Life Table		P=0.298	P=0.364	P=0.386
Incidental Tumor Test		P=0.411	P=0.432	P=0.524
Cochran-Armitage Trend Test		P=0.412		
Fisher Exact Test			P=0.500	P=0.500
Hematopoietic System: Lymphoma, All Malignant				
Tumor Rates				
Overall *(a)*	3/50 (6%)	5/50 (10%)	9/50 (18%)	7/50 (14%)
Adjusted *(b)*	8.6%	11.2%	27.5%	19.0%
Terminal *(c)*	3/35 (9%)	2/39 (5%)	5/28 (18%)	2/29 (7%)
Statistical Tests *(d)*				
Life Table		P=0.203	P=0.094	P=0.263
Incidental Tumor Test		P=0.464	P=0.219	P=0.580
Cochran-Armitage Trend Test		P=0.333		
Fisher Exact Test			P=0.194	P=0.380

TABLE I3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Untreated Control	Vehicle Control	30 mg/kg	60 mg/kg
Circulatory System: Hemangiosarcoma				
Tumor Rates				
Overall *(a)*	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted *(b)*	8.1%	4.9%	8.8%	9.6%
Terminal *(c)*	2/35 (6%)	1/39 (3%)	1/28 (4%)	2/29 (7%)
Statistical Tests *(d)*				
Life Table		P=0.312	P=0.400	P=0.392
Incidental Tumor Test		P=0.474	P=0.545	P=0.524
Cochran-Armitage Trend Test		P=0.412		
Fisher Exact Test			P=0.500	P=0.500
Circulatory System: Hemangioma or Hemangiosarcoma				
Tumor Rates				
Overall *(a)*	3/50 (6%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted *(b)*	8.1%	4.9%	12.1%	9.6%
Terminal *(c)*	2/35 (6%)	1/39 (3%)	2/28 (7%)	2/29 (7%)
Statistical Tests *(d)*				
Life Table		P=0.306	P=0.237	P=0.392
Incidental Tumor Test		P=0.458	P=0.348	P=0.524
Cochran-Armitage Trend Test		P=0.417		
Fisher Exact Test			P=0.339	P=0.500
Liver: Adenoma				
Tumor Rates				
Overall *(a)*	7/50 (14%)	5/50 (10%)	5/49 (10%)	5/48 (10%)
Adjusted *(b)*	19.1%	12.4%	17.9%	16.4%
Terminal *(c)*	6/35 (17%)	4/39 (10%)	5/28 (18%)	4/28 (14%)
Statistical Tests *(d)*				
Life Table		P=0.360	P=0.425	P=0.442
Incidental Tumor Test		P=0.400	P=0.474	P=0.511
Cochran-Armitage Trend Test		P=0.539		
Fisher Exact Test			P=0.617	P=0.603
Liver: Carcinoma				
Tumor Rates				
Overall *(a)*	14/50 (28%)	12/50 (24%)	13/49 (27%)	10/48 (21%)
Adjusted *(b)*	36.3%	28.1%	41.0%	31.2%
Terminal *(c)*	11/35 (31%)	9/39 (23%)	10/28 (36%)	7/28 (25%)
Statistical Tests *(d)*				
Life Table		P=0.413	P=0.207	P=0.495
Incidental Tumor Test		P=0.534N	P=0.325	P=0.543N
Cochran-Armitage Trend Test		P=0.404N		
Fisher Exact Test			P=0.477	P=0.447N
Liver: Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	19/50 (38%)	16/50 (32%)	15/49 (31%)	14/48 (29%)
Adjusted *(b)*	49.6%	37.7%	47.6%	42.4%
Terminal *(c)*	16/35 (4%)	13/39 (33%)	12/28 (43%)	10/28 (36%)
Statistical Tests *(d)*				
Life Table		P=0.332	P=0.288	P=0.394
Incidental Tumor Test		P=0.471	P=0.419	P=0.547
Cochran-Armitage Trend Test		P=0.423N		
Fisher Exact Test			P=0.527N	P=0.466N

TABLE I3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Untreated Control	Vehicle Control	30 mg/kg	60 mg/kg
Adrenal: Pheochromocytoma				
Tumor Rates				
Overall *(a)*	1/46 (2%)	2/50 (4%)	3/47 (6%)	0/47 (0%)
Adjusted *(b)*	2.6%	4.8%	10.0%	0.0%
Terminal *(c)*	0/34 (0%)	1/39 (3%)	2/28 (7%)	0/28 (0%)
Statistical Tests *(d)*				
Life Table		P=0.291N	P=0.379	P=0.297N
Incidental Tumor Test		P=0.209N	P=0.470	P=0.221N
Cochran-Armitage Trend Test		P=0.219N		
Fisher Exact Test			P=0.470	P=0.263N

(a) Number of tumor bearing animals/number of animals examined at the site.

(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.

(c) Observed tumor incidence at terminal kill.

(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. 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 I4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Sarcoma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted *(b)*	0.0%	4.7%	6.5%	7.1%
Terminal *(c)*	0/37 (0%)	1/40 (3%)	0/41 (0%)	1/38 (3%)
Statistical Tests *(d)*				
Life Table		P=0.385	P=0.483	P=0.479
Incidental Tumor Test		P=0.502	P=0.347	P=0.640
Cochran-Armitage Trend Test		P=0.412		
Fisher Exact Test			P=0.500	P=0.500
Lung: Alveolar/Bronchiolar Adenoma				
Tumor Rates				
Overall *(a)*	3/49 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	8.1%	2.5%	2.4%	7.9%
Terminal *(c)*	3/37 (8%)	1/40 (3%)	1/41 (2%)	3/38 (8%)
Statistical Tests *(d)*				
Life Table		P=0.187	P=0.756N	P=0.287
Incidental Tumor Test		P=0.187	P=0.756N	P=0.287
Cochran-Armitage Trend Test		P=0.202		
Fisher Exact Test			P=0.753	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	4/49 (8%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted *(b)*	10.8%	2.5%	4.5%	13.2%
Terminal *(c)*	4/37 (11%)	1/40 (3%)	1/41 (2%)	5/38 (13%)
Statistical Tests *(d)*				
Life Table		P=0.052	P=0.501	P=0.091
Incidental Tumor Test		P=0.050	P=0.459	P=0.091
Cochran-Armitage Trend Test		P=0.060		
Fisher Exact Test			P=0.500	P=0.102
Hematopoietic System: Malignant Lymphoma, Histiocytic Type				
Tumor Rates				
Overall *(a)*	6/50 (12%)	6/50 (12%)	1/50 (2%)	4/50 (8%)
Adjusted *(b)*	13.8%	13.1%	2.4%	8.8%
Terminal *(c)*	2/37 (5%)	3/40 (7%)	1/41 (2%)	1/38 (3%)
Statistical Tests *(d)*				
Life Table		P=0.316N	P=0.065N	P=0.412N
Incidental Tumor Test		P=0.186N	P=0.059N	P=0.274N
Cochran-Armitage Trend Test		P=0.283N		
Fisher Exact Test			P=0.056N	P=0.370N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type				
Tumor Rates				
Overall *(a)*	6/50 (12%)	4/50 (8%)	8/50 (16%)	6/50 (12%)
Adjusted *(b)*	15.2%	9.6%	18.2%	15.8%
Terminal *(c)*	5/37 (14%)	3/40 (7%)	6/41 (15%)	6/38 (16%)
Statistical Tests *(d)*				
Life Table		P=0.290	P=0.188	P=0.338
Incidental Tumor Test		P=0.276	P=0.184	P=0.326
Cochran-Armitage Trend Test		P=0.322		
Fisher Exact Test			P=0.178	P=0.370

TABLE I4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Hematopoietic System: Lymphoma, All Malignant				
Tumor Rates				
Overall *(a)*	17/50 (34%)	11/50 (22%)	11/50 (22%)	12/50 (24%)
Adjusted *(b)*	38.1%	23.6%	24.6%	27.8%
Terminal *(c)*	10/37 (27%)	6/40 (15%)	8/41 (20%)	8/38 (21%)
Statistical Tests *(d)*				
Life Table		P=0.397	P=0.584	P=0.440
Incidental Tumor Test		P=0.441	P=0.563	P=0.489
Cochran-Armitage Trend Test		P=0.452		
Fisher Exact Test			P=0.595	P=0.500
Hematopoietic System: Lymphoma or Leukemia				
Tumor Rates				
Overall *(a)*	17/50 (34%)	12/50 (24%)	11/50 (22%)	12/50 (24%)
Adjusted *(b)*	38.1%	25.5%	24.6%	27.8%
Terminal *(c)*	10/37 (27%)	6/40 (15%)	8/41 (20%)	8/38 (21%)
Statistical Tests *(d)*				
Life Table		P=0.485	P=0.505N	P=0.526
Incidental Tumor Test		P=0.531	P=0.555N	P=0.576
Cochran-Armitage Trend Test		P=0.547		
Fisher Exact Test			P=0.500N	P=0.592
Circulatory System: Hemangiosarcoma				
Tumor Rates				
Overall *(a)*	0/50 (0%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted *(b)*	0.0%	7.0%	4.9%	2.3%
Terminal *(c)*	0/37 (0%)	2/40 (5%)	2/41 (5%)	0/38 (0%)
Statistical Tests *(d)*				
Life Table		P=0.245N	P=0.501N	P=0.335N
Incidental Tumor Test		P=0.264N	P=0.527N	P=0.360N
Cochran-Armitage Trend Test		P=0.222N		
Fisher Exact Test			P=0.500N	P=0.309N
Circulatory System: Hemangioma or Hemangiosarcoma				
Tumor Rates				
Overall *(a)*	1/50 (2%)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted *(b)*	2.7%	9.4%	6.9%	4.8%
Terminal *(c)*	1/37 (3%)	3/40 (7%)	2/41 (5%)	1/38 (3%)
Statistical Tests *(d)*				
Life Table		P=0.294N	P=0.502N	P=0.370N
Incidental Tumor Test		P=0.319N	P=0.553N	P=0.393N
Cochran-Armitage Trend Test		P=0.264N		
Fisher Exact Test			P=0.500N	P=0.339N
Liver: Carcinoma				
Tumor Rates				
Overall *(a)*	4/48 (8%)	1/50 (2%)	5/50 (10%)	1/50 (2%)
Adjusted *(b)*	10.8%	2.5%	11.4%	2.6%
Terminal *(c)*	4/37 (11%)	1/40 (3%)	3/41 (7%)	1/38 (3%)
Statistical Tests *(d)*				
Life Table		P=0.570	P=0.108	P=0.750
Incidental Tumor Test		P=0.544	P=0.079	P=0.750
Cochran-Armitage Trend Test		P=0.594		
Fisher Exact Test			P=0.102	P=0.753

TABLE I4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Liver: Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	8/48 (17%)	2/50 (4%)	7/50 (14%)	2/50 (4%)
Adjusted *(b)*	20.9%	5.0%	16.1%	5.3%
Terminal *(c)*	7/37 (19%)	2/40 (5%)	5/41 (12%)	2/38 (5%)
Statistical Tests *(d)*				
Life Table		P=0.546	P=0.087	P=0.676
Incidental Tumor Test		P=0.525	P=0.067	P=0.676
Cochran-Armitage Trend Test		P=0.576		
Fisher Exact Test			P=0.080	P=0.691
Pituitary: Adenoma				
Tumor Rates				
Overall *(a)*	5/41 (12%)	4/39 (10%)	1/38 (3%)	3/38 (8%)
Adjusted *(b)*	15.1%	12.1%	3.2%	9.7%
Terminal *(c)*	4/31 (13%)	4/33 (12%)	1/31 (3%)	3/31 (10%)
Statistical Tests *(d)*				
Life Table		P=0.441N	P=0.197N	P=0.535N
Incidental Tumor Test		P=0.441N	P=0.197N	P=0.535N
Cochran-Armitage Trend Test		P=0.424N		
Fisher Exact Test			P=0.187N	P=0.515N
Pituitary: Adenoma or Carcinoma				
Tumor Rates				
Overall *(a)*	5/41 (12%)	4/39 (10%)	1/38 (3%)	4/38 (11%)
Adjusted *(b)*	**15.1%**	12.1%	3.2%	11.6%
Terminal *(c)*	**4/31 (13%)**	4/33 (12%)	1/31 (3%)	3/31 (10%)
Statistical Tests *(d)*				
Life Table		P=0.553	P=0.197N	P=0.611
Incidental Tumor Test		P=0.441N	P=0.197N	P=0.535N
Cochran-Armitage Trend Test		P=0.571		
Fisher Exact Test			P=0.187N	P=0.629
Uterus: Endometrial Stromal Polyp				
Tumor Rates				
Overall *(a)*	1/48 (2%)	3/50 (6%)	1/50 (2%)	2/48 (4%)
Adjusted *(b)*	2.7%	7.5%	2.3%	4.9%
Terminal *(c)*	1/37 (3%)	3/40 (7%)	0/41 (0%)	1/37 (3%)
Statistical Tests *(d)*				
Life Table		P=0.433N	P=0.308N	P=0.536N
Incidental Tumor Test		P=0.456N	P=0.336N	P=0.551N
Cochran-Armitage Trend Test		P=0.415N		
Fisher Exact Test			P=0.309N	P=0.520N
Uterus: Leiomyosarcoma				
Tumor Rates				
Overall *(a)*	2/48 (4%) *(e)*	0/50 (0%)	3/50 (6%)	0/48 (0%)
Adjusted *(b)*	4.7%	0.0%	7.1%	0.0%
Terminal *(c)*	1/37 (3%)	0/40 (0%)	2/41 (5%)	0/37 (0%)
Statistical Tests *(d)*				
Life Table		P=0.621	P=0.123	*(f)*
Incidental Tumor Test		P=0.600	P=0.102	*(f)*
Cochran-Armitage Trend Test		P=0.629		
Fisher Exact Test			P=0.121	*(f)*

TABLE I4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. 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) One animal also had a leiomyoma.
(f) Not significant. No tumors in dosed or control groups.

APPENDIX J

SENTINEL ANIMAL SEROLOGY DATA FOR THE CHLOROBENZENE BIOASSAY

APPENDIX J

The serum samples of sentinel animals were evaluated for antibodies to the following viruses.

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 - Ectromelia (Mouse Pox) Virus
Sendai - Sendai Virus
M.Ad - Mouse Adenovirus
MHV - Mouse Hepatitis Virus
LCM - Lymphocytic Choriomeningitis Virus

Rats

PVM
KRV - Kilham Rat Virus
H-1 - Toolan's H-1 Virus
Sendai
RCV - Rat Corona Virus - Sialodacryoadenitis Virus (RCV - SDAV)

Serum samples were evaluated for antibodies to all the viruses listed above for each species. Only the positive results (antibody titers) are presented in the accompanying Table.

Abbreviations used for tests to determine antibody titers are:

HI - Hemagglutination Inhibition Test
CF - Complement Fixation Test
ELISA - Enzyme Linked Immunosorbant Assay

TABLE J1. SUMMARY OF VIRAL ANTIBODY TITERS

	Mice					Rats
	PVM (HI)	GDVII (HI)	MVM (HI)	Sendai (CF)	MHV (CF)	KRV (HI)
Six Months						
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	10	—
F	—	—	—	—	TC	—
F	—	—	—	—	—	—
Twelve Months						
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
M	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	20	—	—
Eighteen Months						
M	20	—	—	—	—	—
M	—	—	—	—	—	—
M	20	—	40	—	—	—
M	—	—	—	—	—	—
M	—	—	20	—	—	—
F	—	—	20	—	—	—
F	20	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
F	—	—	—	—	—	—
Twenty Four Months						
M	—	—	—	—	AC	80
M	—	—	A	—	10	80
M	—	—	—	—	10	—
M	—	40	—	—	—	—
M	—	20	—	—	10	40
F	—	—	—	—	—	80
F	—	40	—	—	—	—
F	—	—	—	—	—	—
F	—	A	A	—	AC	40
F	—	—	—	—	—	80
Significant titer	20	20	20	10	10	20

M - Male
F - Female
A - Serum agglutinates red blood cells
TC - Serum reacts with control antigen
AC - Anticomplementary serum

APPENDIX K

MUTAGENICITY TESTING OF CHLOROBENZENE

APPENDIX K

Chlorobenzene was tested and evaluated blind in each of the four tester strains of *Salmonella typhimurium* using a preincubation modification (Yahagi et al., 1975) of the *Salmonella* assay (Ames et al., 1975). Strains of TA98 and TA1537 are more sensitive to chemicals that exhibit frameshift mutagenic activity; strain TA1535 is more sensitive to chemicals that cause base-pair substitutions. Strain TA100 reverts by a variety of frameshift and base-pair substitution mutagens. Strain TA100 has lost its specificity for base-pair substitution mutagens because of the addition of the plasmid (pK101). Consequently, TA100 is not more sensitive to chemicals that cause base-pair substitution mutations.

Chlorobenzene was solubilized in dimethyl sulfoxide (DMSO) and was incubated with the tester strains in suspension culture (20 minutes at 37°C). Soft agar was added, and the mixture was plated to detect revertant colonies. The colonies that are counted are not mutants. (They are mutant for some markers, but not for histidine, which is the marker that is being selected for prototrophy.) Thus, they are called revertants, not mutants. This is a reverse-mutation test, not a forward-mutation test. Exogenous metabolic activation was provided by liver S-9 preparations from Aroclor-1254 ®-induced Sprague-Dawley rats and Syrian hamsters. Coded chemicals were tested at five doses in triplicate in each strain and were retested at least 1 week later.

TABLE K1. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA100 AT CASE WESTERN RESERVE UNIVERSITY TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate		
	Test I	Test II	Test III
A. No Activation			
0	153 ± 2.0	94 ± 1.9	84 ± 7.3
3.3	—	97 ± 2.0	79 ± 10.4
10.0	—	106 ± 7.7	86 ± 4.5
33.0	—	104 ± 7.4	81 ± 6.9
100.0	128 ± 2.5	105 ± 5.7	83 ± 7.1
333.0	—	86 ± 1.3	62 ± 9.3
1,000.0	t *(b)*	—	—
10,000.0	56	—	—
11,243.0	138	—	—
Positive Control	436 ± 7.0	343 ± 16.6	654 ± 34.9
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation			
0.0	121 ± 2.9	135 ± 7.4	—
3.3	122 ± 6.6	131 ± 6.2	—
10.0	121 ± 9.8	131 ± 3.2	—
33.0	111 ± 8.7	130 ± 8.1	—
100.0	176 ± 77.4	100 ± 6.4	—
333.0	109 ± 11.7	109 ± 6.5	—
Positive Control	433 ± 20.7	830 ± 50.7	—
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation			
0.0	110 ± 3.8	120 ± 5.1	—
3.3	143 ± 15.1	134 ± 12.4	—
10.0	142 ± 8.6	135 ± 11.3	—
33.0	129 ± 6.9	119 ± 12.2	—
100.0	147 ± 4.1	110 ± 5.4	—
333.0	142 ± 4.6	109 ± 10.8	—
Positive Control	555 ± 17.7	1019 ± 108.8	—

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

(b) t = toxic (cytotoxic) to bacteria (subjective analysis)

TABLE K2. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA1535 AT CASE WESTERN RESERVE UNIVERSITY TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	7 ± 0.3	6 ± 0.6
3.3	7 ± 2.7	5 ± 0.3
10.0	6 ± 1.2	5 ± 0.0
33.0	7 ± 2.0	6 ± 0.3
100.0	7 ± 0.9	6 ± 0.3
333.0	6 ± 2.4	5 ± 0.0
Positive Control	281 ± 4.4	214 ± 38.4
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	9 ± 0.3	8 ± 0.7
3.3	10 ± 1.2	7 ± 1.0
10.0	8 ± 1.2	6 ± 0.6
33.0	8 ± 0.6	6 ± 0.3
100.0	6 ± 0.9	6 ± 0.6
333.0	7 ± 2.6	6 ± 0.3
Positive Control	22 ± 3.4	42 ± 12.5
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	10 ± 0.6	8 ± 1.2
3.3	6 ± 0.9	7 ± 1.9
10.0	8 ± 1.5	6 ± 0.9
33.0	7 ± 2.0	6 ± 0.6
100.0	10 ± 0.9	7 ± 0.7
333.0	8 ± 1.3	6 ± 0.3
Positive Control	39 ± 5.9	51 ± 6.4

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

TABLE K3. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA1537 AT CASE WESTERN RESERVE UNIVERSITY TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	2 ± 0.3	3 ± 0.6
3.3	3 ± 0.7	4 ± 0.7
10.0	3 ± 1.0	4 ± 0.7
33.0	3 ± 0.3	4 ± 0.7
100.0	5 ± 2.4	5 ± 1.7
333.0	4 ± 1.8	4 ± 1.0
Positive Control	137 ± 11.7	156 ± 8.6
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	5 ± 1.2	6 ± 0.6
3.3	9 ± 3.2	7 ± 1.9
10.0	6 ± 1.3	6 ± 0.3
33.0	6 ± 0.9	5 ± 0.9
100.0	5 ± 0.9	6 ± 0.3
333.0	8 ± 0.3	6 ± 2.0
Positive Control	29 ± 6.8	80 ± 6.4
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	6 ± 0.9	7 ± 0.6
3.3	6 ± 1.3	6 ± 0.6
10.0	6 ± 0.9	6 ± 0.7
33.0	4 ± 0.3	6 ± 0.3
100.0	9 ± 2.9	7 ± 1.9
333.0	6 ± 3.1	6 ± 0.6
Positive Control	37 ± 9.7	72 ± 4.5

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

TABLE K4. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA98 AT CASE WESTERN RESERVE UNIVERSITY TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	14 ± 0.3	18 ± 2.3
3.3	16 ± 1.5	18 ± 3.2
10.0	12 ± 3.5	16 ± 1.7
33.0	15 ± 3.2	14 + 2.7
100.0	10 ± 0.7	14 ± 0.7
333.0	10 ± 1.5	11 ± 1.0
Positive Control	120 ± 14.4	344 ± 23.1
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	19 ± 2.0	25 ± 3.2
3.3	22 ± 2.5	25 ± 2.6
10.0	38 ± 18.7	21 ± 3.0
33.0	19 ± 2.4	20 ± 3.2
100.0	18 ± 2.9	20 ± 4.2
333.0	19 ± 5.2	25 ± 0.3
Positive Control	370 ± 15.9	913 ± 89.3
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	20 ± 5.8	22 ± 2.3
3.3	25 ± 3.3	20 ± 4.0
10.0	19 ± 4.7	20 ± 3.0
33.0	19 ± 2.3	24 ± 3.0
100.0	22 ± 2.7	27 ± 1.2
333.0	20 ± 7.1	15 ± 3.6
Positive Control	436 ± 19.1	1086 ± 38.4

The data are represented as revertant colonies per plate, $\bar{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

TABLE K5. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA100 AT STANFORD RESEARCH INSTITUTE TESTING *FACILITY*

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	111 ± 4.4	92 ± 12.6
33.3	117 ± 5.6	102 ± 7.5
100.0	103 ± 6.0	89 ± 6.7
333.3	95 ± 8.0	81 + 8.6
666.7	–	93 ± 9.4
1000.0	93 ± 5.7 s *(b)*	76 ± 12.5 s
3333.3	t *(c)*	—
Positive Control	400 ± 5.8	416 ± 11.3
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	104 ± 5.3	123 ± 4.9
33.3	112 ± 6.9	86 ± 7.5
100.0	107 ± 8.7	88 ± 5.8
333.3	94 ± 3.2	78 ± 6.6
1000.0	80 ± 9.8 s	74 ± 12.1 s
3333.3	35 ± 2.0 s	9 ± 9.3 s
Positive Control	867 ± 37.5	549 ± 71.3
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	113 ± 5.9	98 ± 6.7
33.3	105 ± 5.8	103 ± 8.4
100.0	91 ± 10.1	92 ± 3.5
333.3	96 ± 2.3	103 ± 5.2
1000.0	93 ± 5.0	95 ± 4.5
3333.3	65 ± 16.3 s	77 ± 1.2 s
Positive Control	1980 ± 10.9	2115 ± 14.6

The data are represented as revertant colonies per plate, $\bar{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO ▫ dimethyl sulfoxide (vehicle)

(b) s = Slightly toxic (cytotoxic) to bacteria (subjective analysis).

(c) t = Toxic (cytotoxic) to bacteria (subjective analysis).

TABLE K6. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA1535 AT STANFORD RESEARCH INSTITUTE TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	18 ± 1.5	20 ± 4.4
33.3	28 ± 1.5	18 ± 1.3
100.0	24 ± 4.3	17 ± 2.6
333.3	14 ± 2.9	17 + 1.3
666.7	—	18 ± 4.7
1000.0	22 ± 3.2 s *(b)*	19 ± 4.1 s
3333.3	t *(c)*	—
Positive Control	324 ± 3.3	346 ± 14.4
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	12 ± 2.3	8 ± 1.7
33.3	9 ± 1.8	9 ± 3.4
100.0	8 ± 2.7	12 ± 1.8
333.3	8 ± 0.3	11 ± 0.9
1000.0	10 ± 1.2	14 ± 1.9 s
3333.3	0 ± 0.0 s	0 ± 0.0 s
Positive Control	269 ± 2.3	167 ± 4.9
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	12 ± 2.2	10 ± 1.7
33.3	14 ± 1.7	11 ± 2.3
100.0	12 ± 3.8	9 ± 2.1
333.3	14 ± 1.2	10 ± 1.7
1000.0	14 ± 3.0	10 ± 1.8
3333.3	7 ± 2.0 s	8 ± 3.0 s
Positive Control	243 ± 23.8	266 ± 9.5

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

(b) s = Slightly toxic (cytotoxic) to bacteria (subjective analysis).

(c) t = Toxic (cytotoxic) to bacteria (subjective analysis).

TABLE K7. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA1537 AT STANFORD RESEARCH INSTITUTE TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	14 ± 0.9	5 ± 1.7
33.3	18 ± 4.1	5 ± 1.2
100.0	17 ± 2.2	6 ± 2.1
333.3	8 ± 0.9	5 ± 0.7
666.7	—	4 ± 1.2
1000.0	5 ± 0.3 s *(b)*	t
3333.3	t *(c)*	—
Positive Control	189 ± 16.5	847 ± 54.3
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	25 ± 2.3	6 ± 1.2
33.3	16 ± 2.0	6 ± 1.2
100.0	11 ± 2.3	5 ± 0.9
333.3	12 ± 0.0	5 ± 1.2
1000.0	12 ± 1.7	3 ± 0.3 s
3333.3	6 ± 1.5 s	t
Positive Control	448 ± 11.9	239 ± 24.6
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	24 ± 1.5	8 ± 1.3
33.3	18 ± 3.0	9 ± 2.1
100.0	20 ± 1.9	6 ± 1.2
333.3	22 ± 2.5	5 ± 1.9
1000.0	18 ± 0.9	5 ± 0.6
3333.3	10 ± 4.6 s	1 ± 0.7 s
Positive Control	429 ± 17.2	411 ± 10.3

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

(b) s = Slightly toxic (cytotoxic) to bacteria (subjective analysis).

(c) t = Toxic (cytotoxic) to bacteria (subjective analysis).

TABLE K8. RESULTS OF MUTAGENICITY TESTS OF CHLOROBENZENE IN *SALMONELLA TYPHIMURIUM* TA98 AT STANFORD RESEARCH INSTITUTE TESTING FACILITY

Dose (μg/plate) (DMSO) *(a)*	Number of Revertants per Plate	
	Test I	Test II
A. No Activation		
0.0	24 ± 2.6	34 ± 4.5
33.3	21 ± 1.5	21 ± 2.6
100.0	23 ± 1.8	27 ± 3.5
333.3	16 ± 2.7	22 + 3.4
666.7	—	24 ± 1.7
1000.0	14 ± 2.3 s *(b)*	20 ± 3.9 s
3333.3	t *(c)*	—
Positive Control	718 ± 58.2	671 ± 57.5
B. Preincubation with Aroclor-1254® Induced Sprague-Dawley Rat Liver S-9 Preparation		
0.0	37 ± 6.7	43 ± 1.0
33.3	30 ± 0.9	28 ± 1.7
100.0	36 ± 4.1	31 ± 2.0
333.3	23 ± 3.5	24 ± 2.6
1000.0	26 ± 5.5	10 ± 4.7 s
3333.3	3 ± 1.8 s	t
Positive Control	427 ± 4.3	365 ± 22.9
C. Preincubation with Aroclor-1254® Induced Syrian Hamster Liver S-9 Preparation		
0.0	45 ± 4.0	33 ± 2.3
33.3	36 ± 1.9	35 ± 3.6
100.0	30 ± 5.5	33 ± 3.2
333.3	30 ± 2.2	31 ± 2.9
1000.0	25 ± 2.6	27 ± 1.8
3333.3	21 ± 2.1 s	t
Positive Control	1321 ± 18.8	1271 ± 7.8

The data are represented as revertant colonies per plate, $\overline{X}$ ± S.E.; positive control chemicals and doses are shown in table K9.

(a) DMSO = dimethyl sulfoxide (vehicle)

(b) s = Slightly toxic (cytotoxic) to bacteria (subjective analysis).

(c) t = Toxic (cytotoxic) to bacteria (subjective analysis).

TABLE K9. *SALMONELLA* POSITIVE CONTROLS

Testing Laboratory	Strain	Chemical and Dose (μg/plate)		
		Nonactivate	Rat Liver	Hamster Liver
SRI	TA100	NaAz, 1	2-AA, 1	2-AA, 1
CWR	TA100	NaAz, 3	2-AA, 1	2-AA, 1
SRI	TA1535	NaAz, 1	2-AA, 2.5	2-AA, 2.5
CWR	TA1535	NaAz, 1	2-AA, 1	2-AA, 1
SRI	TA1537	9-AA, 50	2-AA, 2.5	2-AA, 2.5
CWR	TA1537	9-AA, 33	2-AA, 1	2-AA, 1
SRI	TA98	NoPD, 5	2-AA, 1	2-AA, 1
CWR	TA98	NoPD, 3.3	2-AA, 1	2-AA, 1

NaAz = Sodium Azide
2-AA = 2-Aminoanthracene
9-AA = 9-Aminoacridine
NoPD = 4-Nitro-o-phenylenediamine
SRI = Stanford Research Institute
CWR = Case Western Reserve University

APPENDIX L

CHEMICAL ANALYSIS OF CHLOROBENZENE

APPENDIX L

A. ELEMENTAL ANALYSIS

Element	C	H	Cl
Theory	64.02	4.48	31.50
Determined	64.02 64.15	4.58 4.62	31.29 31.39

B. WATER ANALYSIS (Karl Fischer)

<0.03%

C. TITRATION FOR ACIDIC COMPONENTS

1.2 ± 0.2 (δ) ppm (assumed to be HCl)

D. BOILING POINT

Determined	Literature Value
129 ± 1 (δ)°C at 727 torr (visual, micro boiling point)	131°-132°C (Merck, 1976)
132.8°-133°C (Dupont 900 DTA)	

E. INDEX OF REFRACTION

Determined	Literature Value
n_D^{20} : 1.5238 ± 0.0003 (δ)	n_D^{20} : 1.5248 (Merck, 1976)

F. DENSITY

Determined	Literature Value
$d_{22}^{24.5}$: 1.1027 ± 0.0006 (δ) g/ml	n_4^{20} : 1.107 g/ml (Merck, 1976)

G. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 230°C
Detector temperature: 275°C

1. System 1

   Column: 20% SP 2100/0.1% Carbowax 1500 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
   Oven Temperature program: 50°C, 5 min; 50°-170°C at 10°C/min
   Sample injected: 5 μl neat, diluted to 1% and 0.5% in pentane to measure area of major peak
   Results: Major peak and 11 impurities. The areas of the impurities total less than 0.1% of the area of the major peak.

APPENDIX L

Peak	Retention Time (min)	Retention Time (Relative to Chlorobenzene)	Area (Percent of Chlorobenzene)
1	1.5	0.14	<0.001
2	2.7	0.26	<0.001
3	3.4	0.32	<0.001
4	3.9	0.36	<0.002
5	5.1	0.48	<0.001
6	7.9	0.75	<0.001
7	9.5	0.89	<0.002
8	10.6	1.00	100
9	11.5	1.08	shoulder, <0.02
10	11.9	1.12	shoulder, <0.02
11	12.8	1.20	0.03
12	13.2	1.24	0.002

2. System 2

Column: 10% Carbowax 20M - TPA on 80/100
Chromosorb W AW, 1.8 m x 4 mm I.D., glass
Oven temperature program: 50°C, 5 min; 50°-200°C
at 10°C/min
Sample injected: 4 μl neat, diluted to 1% and 0.5%
in methanol to measure area of major peak
Results: Major peak and 15 impurities. The areas of the impurities
total less than 0.03% of the area of the major peak.
15 impurities total less than 0.03% of the area of the major peak.

Peak	Retention Time (min)	Retention Time (Relative to Chlorobenzene)	Area (Percent of Chlorobenzene)
1	0.9	0.10	0.0002
2	1.1	0.11	0.0005
3	1.4	0.15	<0.0003
4	1.6	0.16	0.0003
5	1.9	0.20	0.002
6	2.6	0.27	0.0004
7	3.2	0.33	0.001
8	3.6	0.37	0.0002
9	4.0	0.42	<0.0002
10	9.6	1.00	100
11	11.2	1.16	shoulder, 0.06
12	11.4	1.18	shoulder, 0.02
13	11.8	1.22	0.002
14	12.7	1.31	0.0005
15	13.0	1.35	0.01
16	13.5	1.40	0.0008

H. SPECTRAL DATA

(1) Infrared

Instrument: Beckman IR-12
Cell: 0.054 mm liquid cell, sodium chloride windows
Results: See Figure 6

Peak in literature spectrum at approximately 800 cm-1 not observed in this sample. In other respects this spectrum is consistent with the literature spectrum (Sadtler Standard Spectra).

(2) Ultraviolet/Visible

Instrument: Cary 118

Literature values calculated from graph (Sadtler Standard Spectra)

λ max (nm)	ε x 10	λ max	ε x 10
272	18.2 ± 0.4 (δ)	271	20.9
268 shoulder	12.8 ± 0.4 (δ)	267	14.1
264.5	24.3 ± 0.4 (δ)	264	25.8
261	17.0 ± 0.4 (δ)	261	17.7
258	18.8 ± 0.4 (δ)	257	19.8
255 shoulder	13.4 ± 0.8 (δ)	255 shoulder	14.1
251	12.3 ± 0.4 (δ)	251	12.8
245	7.4 ± 0.4 (δ)	245	7.7
240	4.1 ± 0.5 (δ)	239	4.0
233	2.7 ± 0.6 (δ)	233	2.4
219	604 ± 10 (δ)	219	800
215	771 ± 12 (δ)	215.5	1,090
211	734 ± 12 (δ)	210	1,040

No absorbance between 350 and 800 nm (visible range) at a concentration of 1% v/v.

Solvent: Hexane

Solvent: Isooctane

(3) Nuclear Magnetic Resonance

Instrument: Varian HA-100

Consistent with literature spectrum (Sadtler Standard Spectra)

Solvent: Neat, tetramethylsilane added
Assignments: See Figure 7
(a) m, δ 6.82-7.22 ppm
Integration Ratio:
(a) 5.00

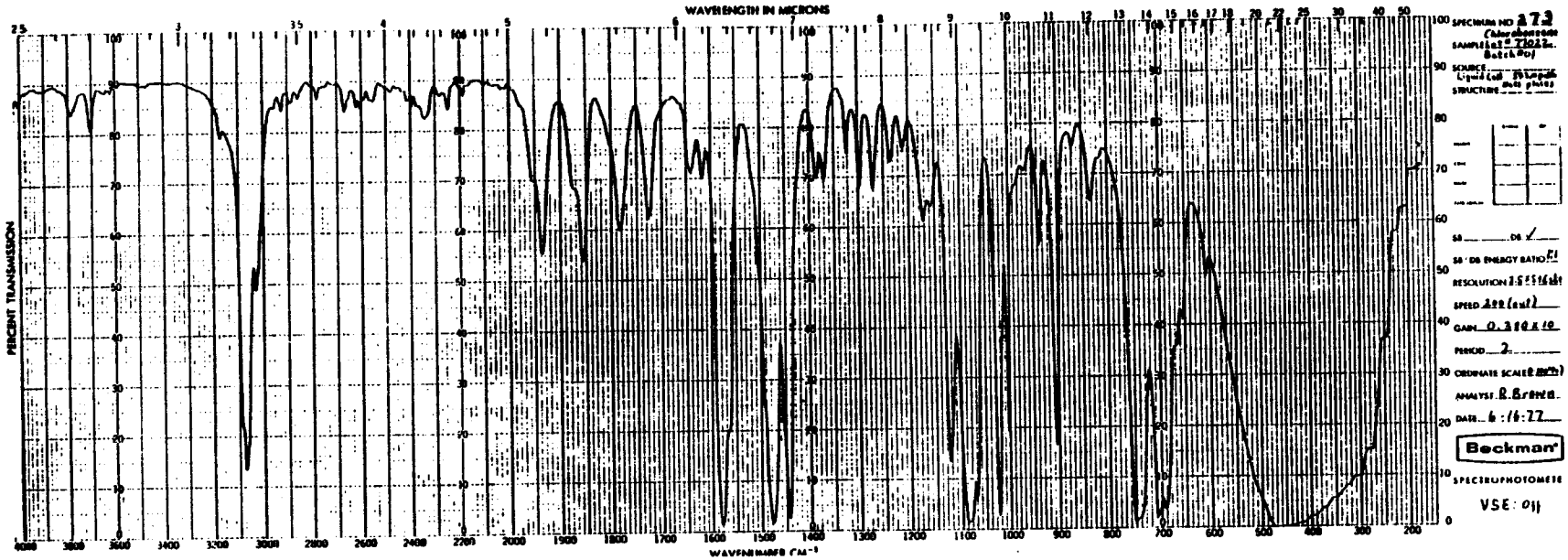

Figure 8. Infrared Absorption Spectrum of Chlorobenzene (Lot No. 77022)

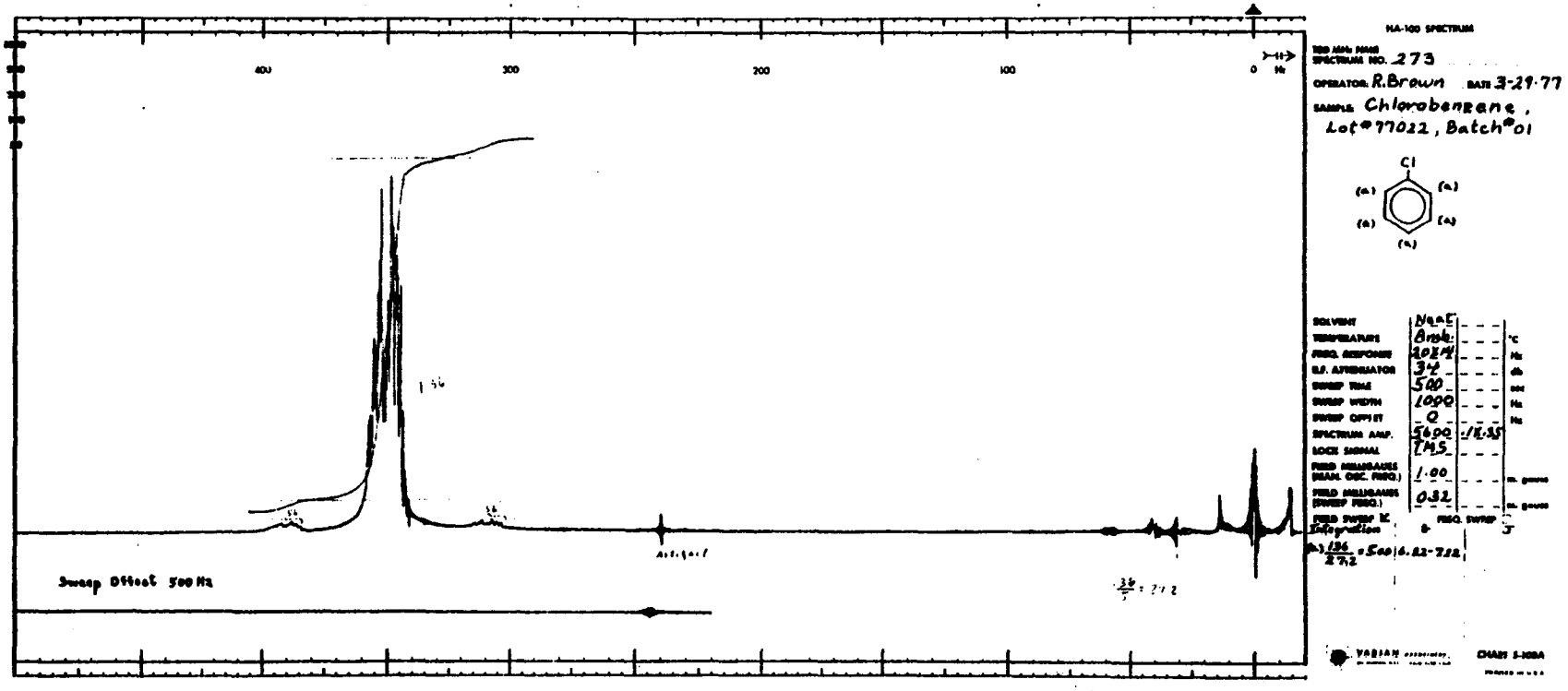

Figure 7. Nuclear Magnetic Resonance Spectrum of Chlorobenzene (Lot No. 77022)

APPENDIX M

ANALYSIS OF CHLOROBENZENE IN CORN OIL FOR STABILITY OF CHLOROBENZENE

A. SAMPLE PREPARATION: Solutions of chlorobenzene in corn oil (2.25%, w/v) were prepared in duplicate for storage of 0, 3, 4, 5, 6, and 7 days, respectively. A typical sample was prepared as follows: 2 ml of corn oil was transferred into an 8.5-ml septum vial and the vial was sealed (Microsep F-138 gas chromatgraphy septa with Teflon film facing, from Canton Bio-Medical Products, Inc.; aluminum crimp seals from Wheaton Scientific Co., Inc.) and weighed. Approximately 45 mg of chlorobenzene was then injected, and the vial was reweighed to determine the exact amount of chlorobenzene added. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature (25°C) for the appropriate time period.

B. EXTRACTION AND ANALYSIS: At the end of each storage time segment, the appropriate samples were extracted with 2 ml of methanol, which was injected into the vials via a 2-ml syringe. The two-phase mixtures were thoroughly shaken and placed in the ultrasonic vibratory bath for 2 minutes. Aliquots for analysis were removed directly from the top (methanol) layer of each sample and analyzed by the following vapor-phase chromatographic system:

Instrument: Varian 2400
Column: 3% OV-225 on 80/100 mesh Supelcoport, 1.9 m x 4 mm I.D., glass
Temperatures:
  Inlet, 155°C;
  Oven, 70°C isothermal;
  Detector, 220°C
Detection: Flame ionization
Retention time of major component: 2.3 min
Carrier gas: Nitrogen; flow rate, 60 cc/min

C. RESULTS:

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture *(a)*
0	2.25 ± 0.08 *(b)*
3	2.25 ± 0.08
4	2.23 ± 0.08
5	2.10 ± 0.08
6	2.23 ± 0.08
7	2.17 ± 0.08

(a) Corrected for a spike recovery of 40% ± 2%.
(b) Original concentration of chlorobenzene in corn oil at time of sample preparation, 2.25%, with a variation among samples of ± 0.05%.

D. CONCLUSION: Chlorobenzene in corn oil at the 2% (w/v) dose level is stable when stored at room temperature (25°C) over a 7-day period.

APPENDIX N

ANALYSIS OF CHLOROBENZENE IN CORN OIL FOR CONCENTRATIONS OF CHLOROBENZENE

APPENDIX N

Standards of chlorobenzene in corn oil at three or four concentrations bracketing the range of sample concentrations were prepared by weighing chlorobenzene and diluting with corn oil. Duplicate one-milliliter aliquots of standards and samples were extracted with methanol. Solutions were vortexed and centrifuged and a portion of the clear methanol layer was removed for analysis by gas chromatography. Concentrations of samples were taken from the linear regression standard curve. Results are presented in Table N1.

TABLE N1. ANALYSIS OF CHLOROBENZENE IN CORN OIL

	Concentration *(a)* of Chlorobenzene in Corn Oil for Target Concentration		
Date Mixed	**6.0 mg/ml**	**12.0 mg/ml**	**24.0 mg/ml**
02/08/79			23.0
			22.7
04/04/79			24.7
06/01/79			25.0
			(23.9) *(b)*
08/23/79			23.8
09/19/79	6.14	11.6	24.4
11/14/79	6.54	11.5	23.2
			(24.7) *(b)*
01/23/80	6.22	11.9	23.5
03/12/80	6.44	12.5	24.8
05/07/80	5.90	12.4	25.3
	(5.84) *(b)*		
08/06/80	5.62	12.0	25.2
08/27/80	6.17	12.7	23.4
10/22/80	6.55	11.8	21.8
12/17/80	6.1	12.2	24.8
		(12.0) *(b)*	
Mean (mg/ml)	6.19	12.1	24.0
Standard deviation	0.303	0.412	1.07
Coefficient of variation (%)	4.90	3.40	4.46
Range (mg/ml)	5.62-6.55	11.5-12.7	21.8-25.3
Number of samples	9	9	14

(a) The data presented are the average of the results of duplicate analyses.
(b) MRI referee analysis

APPENDIX O

SEPARATION AND QUANTITATION OF COPROPORPHYRIN AND UROPORPHYRIN IN URINE

APPENDIX O

A. APPARATUS

Glass Column: 1 cm I.D. and 30 cm long
Spectrophotometer: Aminco-Bowman Spectrophotofluorometer (American Instrument Company, Silver Spring, MD)
Disposable Micropipets: Used to measure the standard porphyrin solution.

B. REAGENTS

Anion-Exchange resin chloride form (Bio-Rad 1x2 200-400 mesh, Bio-Rad Labs., Richmond, CA)

This resin was used as received without further treatment. The resin was allowed to swell in distilled water and was then transferred to columns (containing a small glass-wool plug at the bottom) as a measured volume of slurry, in amount sufficient to give a resin bed that is 10 cm high.

Wash Solvent. This solution contained ethanol:water (15:85 by volume) and 1.0 mol of acetic acid per liter. About 500 ml distilled water, 150 ml of absolute ethanol, and 57 ml of glacial acetic acid, were added to a one-liter volumetric flask and mixed. The mixture was diluted to 1.0 liter with distilled water and stirred.

Coproporphyrin Elution Solvent. To a one-liter volumetric flask were added 500 ml of distilled water and 8.3 ml (0.1 mol) of concentrated hydrochloric acid. After mixing, 250 ml isopropanol (analytical grade) and 100 ml of absolute ethanol were added and mixed. After being diluted to the mark with distilled water, the solution was mixed.

Uroporphyrin Elution Solvent. To a one-liter volumetric flask, about 500 ml of distilled water and 83 ml (10 mol) concentrated hydrochloric acid was added, and the solution was mixed. Two hundred and fifty milliliters of n-propanol (spectro-quality) was added. After mixing, the solution was diluted to the mark with distilled water and mixed.

Standard Porphyrins. The following prophyrins were used: coproporphyrin-I and uroporphyrin-I (Sigma Chemical Company, St. Louis, MO).

C. PROCEDURE (See Sobel et al., 1974; Lavallee and Novellus, 1977)

Before analysis, the column was washed with 20 ml wash solvent and 20 ml distilled water. Three milliliters of urine (taken from 24-hour collection) were added to the column (15 ml slurry volume 10 cm high). The fluid was eluted slowly from the column until the urine level receded to the resin surface. Twenty milliliters of distilled water was added and allowed to drain. Ten milliliters of coproporphyrin eluent was added. The coproporphyrin fraction was collected. When the eluent reached the resin surface, 5 ml of water was added and collection was stopped. Then, the column was rinsed with 20 ml of distilled water and the same procedure was repeated using uroporphyrin eluent.

Aliquots (5 ml) of each fraction were pipetted into a test tube. The solution was diluted to 10 ml with respective eluent and the fluorescence of the porphyrin was recorded. The excitation wavelengths were 404 nm for the coproporphyrin and 410 nm for the uroporphyrin. The fluorescence emission for both porphyrins used was 650 nm.

APPENDIX P

DATA AUDIT SUMMARY

DATA AUDIT SUMMARY

An audit was conducted on the archival data and pathology materials for the 2-year toxicology and carcinogenesis studies of chlorobenzene in rats and mice. These studies were performed at Battelle Columbus Laboratories under a subcontract with Tracor Jitco from the National Cancer Institute. The studies were conducted from January 1979 to February 1981, prior to the requirement of compliance to Good Laboratory Practice standards by NTP in October 1981. The audit was conducted at the NTP Archives, Rockville, Maryland, and involved the following Dynamac personnel: Chris Dippel, M.Phil.; Floris Garner, D.V.M.; Leonard Kiefer, Ph.D.; James Konz, M.S.; James Plautz, M.S.; Ronald Schueler, D.V.M.; and Christine Sexsmith, B.S.

The audit report was reviewed and approved by NTP personnel and is on file at the NTP, Research Triangle Park, NC. The audit consisted of a review of the data and pathology materials collected during the conduct of the study as well as review of the correspondence (e.g., protocol and amendments) and prechronic studies. For the inlife toxicology data, this review involved examination of 100% of the records on animal receipt and husbandry, mortality, environmental conditions, sentinel animals, and dosing. Body weight and clinical observation data for 10% of the animals were examined. In the review of the chemistry portion of the study, all of the records were examined pertaining to receipt and use of the test chemical, analysis of the bulk chemical and dose solutions by the contract laboratory, and characterization of the bulk chemical and analysis of the dose solutions by the reference laboratory. The audit of the pathology materials included review of 100% of the Individual Animal Data Records (IADRs) for correlation between gross and microscopic diagnoses and for clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for 6 of 8 animal groups, and verification of the reported pathology on 10% of the animals.

Review of the inlife toxicology data found several problems that were a result of recordkeeping practices and could not be resolved given the available data. Clinical observations were recorded at irregular intervals, were made using nontechnical terms, and were not followed up by subsequent observations. Eleven discrepancies were found between inlife observations of tissue masses and observations made at necropsy. Some of these were resolved to a certain extent by examination of the wet tissue and by reconsideration of the inlife observations; however, 6 were not resolved satisfactorily and may have been due to inaccurate observations by the inlife technicians. Discrepancies were found in the mortality data; 4 dates of death and 7 modes of death were not recorded in the inlife records and 3 pairs of animals had their identities confused at the time of death. Notations of problems with the automatic watering system were found, either wet cages due to leaking water or observation of dehydrated animals due to lack of water. No mortalities could be associated with these incidents. No information on the prestudy quarantine or data on temperature and humidity were available for review.

Review of the chemistry data found no records for the following: corn oil analysis for peroxide levels, documentation for the analysis by the testing laboratory of the duplicate of the referee sample, and the laboratory notebook for bulk and chemical/vehicle analyses (chromatograms were present).

During the audit of the pathology materials positive identification of the animals by group or individual animal number from the preserved tissues was complicated by the absence of the animals' feet (needed for individual identification) and the general absence of ears (needed for group identification). These were not required to be saved under the study protocol at the time. The most consistent gross observations without microscopic findings were enlarged pituitary and spleen in the rats and enlarged spleen, mesenteric lymph node, and kidney, and cystic ovaries in the mice. During the examination of the wet tissue, 2 subcutaneous masses, one mass adjacent to the colon, and one black focus in the stomach were found in the rats, and 2 nodules or foci in the liver were found in the mice. Minor problems were noted in the tissue accountability, slide/block match, clerical errors, and final table review.

In conclusion, although some problems and discrepancies were identified, these were adequately resolved or were determined not to affect the outcome of the study

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