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TOXICOLOGY AND CARCINOGENESIS STUDIES OF TOLUENE

(CAS NO. 108-88-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF TOLUENE

(CAS NO. 108-88-3)

IN F344/N RATS AND B6C3F1 MICE

(INHALATION STUDIES)

James Huff, Ph.D., Study Scientist

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Public Health Service
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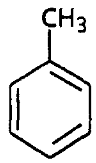

TOLUENE

CAS No. 108-88-3

C_7H_8 Molecular weight 92.1

Synonyms: methylbenzene, toluol, phenylmethane, tolueen (Dutch), toluen (Czech), tolueno (Spanish), toluolo (Italian)

Trade Name: Methacide

ABSTRACT

Toluene (monomethylbenzene) is used to back-blend gasoline, as a chemical intermediate, and as a solvent; 920 million gallons was produced in the United States in 1988. Toxicology studies were conducted by administering toluene (greater than 99% pure) in corn oil by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 13 weeks or by whole-body inhalation exposure for 14 or 15 weeks. Toxicology and carcinogenesis studies were conducted by whole-body inhalation exposure of F344/N rats and $B6C3F_1$ mice of each sex for 15 months or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse L5178Y lymphoma cells, and Chinese hamster ovary cells.

Thirteen-Week Gavage Studies: All rats that received the top dose of 5,000 mg/kg died during the first week, and 8/10 male rats that received 2,500 mg/kg died early. The final mean body weight of male rats that received 2,500 mg/kg was 19% lower than that of vehicle controls. Relative liver, kidney, and heart (female only) weights for rats that received the higher doses were greater than those for vehicle controls. Necrosis of the brain and hemorrhage of the urinary bladder were seen at increased incidences in dosed rats.

All mice that received the top dose of 5,000 mg/kg died during the first week, and 40% of those that received 2,500 mg/kg died before the end of the 13-week gavage studies. The final mean body weight of males at 2,500 mg/kg was 16% lower than that of vehicle controls. At the higher doses, relative liver weights were increased for mice.

Fifteen-Week and Fourteen-Week Inhalation Studies: Eight of 10 male rats exposed at the top exposure concentration of 3,000 ppm died during week 2. Final mean body weights of rats exposed at concentrations of 2,500 or 3,000 ppm were 14%-25% lower than that of controls. As in the gavage studies, the relative liver, kidney, and heart weights for rats exposed at the top two concentrations were increased compared with those for controls. No compound-related effects were seen on sperm; no adverse effects on the estrous cycle were observed.

Five of 10 male mice and all female mice exposed at 3,000 ppm and 70% of female mice at 2,500 ppm died during the first 2 weeks. Final mean body weights of all exposed groups were 7%-13% lower than those of controls. Relative liver weights for mice exposed at 625 ppm or higher, relative lung weights for mice exposed at 1,250 ppm or higher, and relative kidney weights for female mice exposed at 1,250 ppm or higher were greater than those for controls. Centrilobular hypertrophy of the liver was

observed in all male mice exposed at 2,500 ppm and 70% of male mice exposed at 3,000 ppm. No effects on sperm or the estrous cycle were observed.

Fifteen-Month and Two-Year Inhalation Studies: Long-term studies were conducted by exposing groups of 60 rats of each sex to 0, 600, or 1,200 ppm toluene by inhalation, 6.5 hours per day, 5 days per week. Groups of 60 mice of each sex were exposed at 0, 120, 600, or 1,200 ppm on the same schedule. Ten animals per group (except male mice) were removed for toxicologic evaluation after being exposed for 15 months. All other animals were exposed to toluene for 103 weeks.

In the 15-month inhalation studies, the incidences and severity of nonneoplastic lesions of the nasal cavity (degeneration of olfactory and respiratory epithelium and goblet cell hyperplasia) were increased in exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1,200 ppm. The severity of nephropathy was slightly increased in exposed female rats. No chemical-induced neoplasms were observed.

Body Weight and Survival in the Two-Year Studies: Mean body weights of rats and mice were generally similar (yearly averages within 5%) among groups throughout the 2-year studies. No significant differences in survival were observed among rats or mice of either sex, although survival in all groups of male mice was lower than usual (male rats: control, 30/50; 600 ppm, 28/50; 1,200 ppm, 22/50; female rats: 33/50; 35/50; 30/50; male mice: control, 17/60; 120 ppm, 22/60; 600 ppm, 16/60; 1,200 ppm, 19/60; female mice: 30/50; 33/50; 24/50; 32/50). Scrotal, preputial, and penile lesions observed in the male mice were associated with many of the early deaths and with animals killed in a moribund condition.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Nephropathy was seen in almost all rats, and the severity was somewhat increased in exposed rats. A rare renal tubular cell carcinoma in a female rat and an equally uncommon sarcoma of the kidney in another female rat were seen in the 1,200-ppm exposure group. Erosion of the olfactory epithelium and degeneration of the respiratory epithelium were increased in exposed rats. Inflammation of the nasal mucosa and metaplasia of the olfactory epithelium were increased in exposed female rats. A rare squamous cell carcinoma of the nasal mucosa was seen in one female rat at 1,200 ppm. A squamous cell papilloma of the forestomach was observed in one female rat at 1,200 ppm, and a squamous cell carcinoma was observed in a second female rat at 1,200 ppm. No chemically related neoplasms were found in male rats, and the one nasal, two kidney, and two forestomach neoplasms observed in female rats were considered not to be associated with inhalation exposure to toluene.

For mice, no biologically important increases were observed for any nonneoplastic or neoplastic lesions.

Genetic Toxicology: Toluene did not induce gene mutations in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation. In the mouse lymphoma assay, toluene gave an equivocal response with and without exogenous metabolic activation. Toluene did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of exogenous metabolic activation.

Conclusions: Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** for male or female F344/N rats exposed to toluene at concentrations of 600 or 1,200 ppm. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice exposed by inhalation to toluene at concentrations of 120, 600, or 1,200 ppm for 2 years.

SUMMARY OF THE TWO-YEAR INHALATION STUDIES OF TOLUENE

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations			
0, 600, or 1,200 ppm toluene, 6.5 h/d, 5 d/wk	0, 600, or 1,200 ppm toluene, 6.5 h/d, 5 d/wk	0, 120, 600, or 1,200 ppm toluene, 6.5 h/d, 5 d/wk	0, 120, 600, or 1,200 ppm toluene, 6.5 h/d, 5 d/wk
Body weights in the 2-year study			
Exposed and controls similar	Exposed and controls similar	Exposed and controls similar	Exposed and controls similar
Survival rates in the 2-year study			
30/50; 28/50; 22/50	33/50; 35/50; 30/50	17/60; 22/60; 16/60; 19/60	30/50; 33/50; 24/50; 32/50
Nonneoplastic effects			
Nasal cavity: 15 mo--degeneration of olfactory and respiratory epithelium and goblet cell hyperplasia; 2 y--erosion of olfactory epithelium and degeneration of respiratory epithelium and (females only) inflammation of nasal mucosa and metaplasia of olfactory epithelium			
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Toluene is based on 13-week gavage studies that began in May 1981 and ended in August 1981, on 14- and 15-week inhalation studies that began in November 1981 and ended in February 1982, and on 2-year studies that began in September 1982 and ended in October 1984 at International Research and Development Corporation (Mattawan, MI).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on toluene on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of toluene received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J. Huff, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats, no evidence of carcinogenic activity for male or female mice). Dr. Huff also indicated during his remarks that male and female mice might have been able to endure somewhat higher exposure concentrations without having their health or longevity compromised.

Dr. Gallo, a principal reviewer, agreed with the conclusions. He thought that the dose selection for both rats and mice was correct based on organ weight changes and biologic activity after 14-15 weeks of exposure. He stated that discussion on the comparative metabolism of benzene and the alkylbenzenes was excellent, although some discussion on the area of toluene's (and xylene's) modifying the metabolism of benzene would enhance this section.

Dr. Popp, the second principal reviewer, agreed with the conclusions and considered the dose selection quite appropriate based on the available information. He said that the only question of carcinogenicity based on the original pathology concerned the incidence of kidney tumors; thus, the approach of making additional step-sections of the male rat kidney was appropriate and should be commended. Decreased survival in groups of male mice might best be put in perspective in relation to other inhalation studies [see page 53], and the decision not to kill 10 mice from each group at 15 months was proper.

Dr. Lijinsky, the third principal reviewer, opined that the use of the inhalation route of exposure was inappropriate because it prevented a maximum dose from being given to the animals. He noted that short-term studies had been done by the gavage route and asked why this route was not used for the 2-year studies. As a corollary, he commented that a carcinogenic effect was demonstrated by the gavage route for benzene but not by inhalation exposure. Dr. Huff responded that the 14-15 week studies were done by two routes for comparative purposes and the inhalation route was chosen largely because it was particularly relevant to human exposure and because metabolism patterns in rodents were similar by either route. He further noted that Dr. C. Maltoni in Italy has shown multi-organ carcinogenesis for benzene after inhalation exposure. Dr. Huff stated that he would communicate with Dr. Maltoni and attempt to obtain more details about the gavage studies and especially if any toxic and neoplastic lesions were considered to be related to toluene exposure.

There was some discussion about the usefulness of adding 10 animals to some groups to be killed at 15 months. Dr. Scala noted that this had been a recommendation by the NTP Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation in its 1984 report, with the rationale being to obtain a broader look at chronic toxicity unobscured by geriatric changes. Dr. Huff said that this earlier evaluation was also helpful in preparing for evaluations after 2 years by identifying putative target organs early. Dr. Perera suggested that the NTP assess the usefulness of the interim evaluation, and Dr. Huff agreed. Dr. Ashby commented on the finding of five tubular cell adenomas in control male rats after step-sectioning and urged caution in use of data from step-sectioning until there is a fairly large data base.

SUMMARY OF PEER REVIEW COMMENTS (Continued)

Dr. Scala asked if there was more discussion on Dr. Lijinsky's contention that the study was inadequate because a high enough dose was not given. Dr. S. Eustis, NIEHS, said that the evidence of renal toxicity in both male and female rats spoke to there being sufficient exposure. Dr. Ashby thought that the inhalation route was the most appropriate. Dr. R. Griesemer, NIEHS, agreed and said that under the conditions used, the studies were adequately done and reported.

Dr. Gallo moved that the Technical Report on toluene be accepted with the conclusions as written for rats and mice of each sex, no evidence of carcinogenic activity, but with deletion of the statement that "Male and female mice might have been able to endure somewhat higher exposure concentrations without having their health or longevity compromised." Dr. Popp seconded the motion, which was accepted by nine votes and one abstention (Dr. Lijinsky).

I. INTRODUCTION

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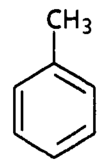


TOLUENE

CAS No. 108-88-3

C_7H_8 Molecular weight 92.1

Synonyms: methylbenzene, toluol, phenylmethane, tolueen (Dutch), toluen (Czech), tolueno (Spanish), toluolo (Italian)

Trade Name: Methacide

The name toluene derives from a natural resin, balsam of Tolu, named for a small town in Colombia (Kirk-Othmer, 1983). Toluene and other alkyl benzenes are single-ring, aromatic compounds containing one or more aliphatic side chains. The major products of commerce and those to which humans are most probably exposed include monomethylbenzene (toluene), ethylbenzene, 1-methylethylbenzene (cumene), and the three dimethylbenzenes (1,2-, 1,3-, and 1,4-xylene) (Andrews and Snyder, 1986). The parent molecule benzene (NTP, 1986a; Huff et al., 1988, 1989) and xylenes, mixed (NTP, 1986b; Huff et al., 1988) have been studied for carcinogenicity. Ethylbenzene is in the short-term study phase by the National Toxicology Program (NTP), and cumene is not being studied for long-term effects. This Technical Report presents the results and evaluative conclusions of the data collected from the short-term and long-term toxicology and carcinogenesis inhalation studies of toluene.

PROPERTIES, PRODUCTION, AND USE

Toluene is a colorless liquid with a benzene-like odor, a boiling point of 110.6° C, a specific gravity of 0.866, a refractive index of 1.497 at 20° C, and a flash point of 4.4° C (closed cup) (Merck, 1983). Toluene is soluble in alcohol, benzene, and ether but is insoluble in water (Condensed Chemical Dictionary, 1981).

Toluene ranked 25th (1986), 23rd (1987), and 24th (1988) in production volume for chemicals produced in the United States; approximately 7 billion pounds was produced in 1987 and 5.8 billion pounds in 1986 (Chem. Eng. News, 1988, 1989). Among organic chemicals, toluene places 13th. Seven billion pounds of toluene was produced in 1987 by 25 companies (USITC, 1988). It is produced by petroleum-refining processes, from by-products of styrene production, and from by-products of coke oven operation (Syracuse Research Corp., 1983). Purified toluene usually contains less than 0.01% benzene, but the industrial grade may contain up to 25% benzene (IPCS, 1985).

Toluene is blended with gasoline and is used as an intermediate in the synthesis of benzoic acid, benzyl and benzoyl derivatives, saccharin, medicines, dyes, perfumes, toluene diisocyanates (polyurethane resins), TNT, and toluene sulfonate detergents; and as a solvent in paints, lacquers, gums, thinners, adhesives, inks, plant resins, and pharmaceutical and cosmetic products (Condensed Chemical Dictionary, 1981; Merck, 1983; FDA, 1984; Fishbein, 1985; USEPA, 1987). Toluene is used in more than 500 cosmetic products (FDA, 1984), which include nail basecoats and undercoats (32 products), nail polish and enamel (501 products), and other manicuring preparations (22 products). Reported concentrations of toluene in these products range from 10%-25% (448 products) to more than 25%-50% (107 products).

EXPOSURE STANDARDS

The current threshold limit value/time-weighted average (TWA) for an 8-hour workday, 40-hour workweek, in the United States is 100 ppm (375 mg/m^3); the short-term exposure limit is 150 ppm (560 mg/m^3) (ACGIH, 1987). The Occupational Safety and Health Administration lists 200 ppm (8-hour TWA), whereas the National Institute for Occupational Safety and Health has promulgated a standard of 100 ppm (10-hour TWA) and of 200 ppm with a 10-minute ceiling. The Immediately Dangerous to Life or Health level is 2,000 ppm (NIOSH, 1985). In 1987, the value for an 8-hour workday was reduced to 50 ppm in several countries (IRPTC, 1987).

ENVIRONMENTAL FATE

Toluene is quite stable in air but can be oxidized in the presence of catalysts to yield benzoic acid. In the presence of heat (or a catalyst) and hydrogen, toluene undergoes dealkylation to produce benzene. Under conditions of water chlorination, toluene may be chlorinated and subsequently hydrolyzed to benzaldehyde. Toluene may undergo photo-oxidation (Shepson et al., 1984) and other photochemical reactions (NRC, 1981; Syracuse Research Corp., 1983). Because of the limited number of studies available, the extent of toluene degradation in soil cannot be determined, although studies with pure cultures indicate that a variety of bacteria and fungi can metabolize toluene and that some organisms can use toluene as a sole source of carbon. A toluene half-life of 20-60 minutes was observed in soil containing toluene-degrading bacteria (USEPA, 1983). Toluene is readily biodegraded in water, both in surface water and during wastewater treatment; however, disappearance of toluene from water is mainly through evaporation.

Evaporation of gasoline and automobile exhaust are the largest combined source of toluene (677 million kg per year) in the environment, and industries that use toluene as a solvent are the second largest source (375 million kg per year); these two sources account for 75% of the toluene emitted to the atmosphere (USEPA, 1983). Nonatmospheric release of toluene to the environment (e.g., to water or soil) is comparatively small and is approximately 0.15% of the total amount emitted to the atmosphere.

Toluene is the most prevalent aromatic hydrocarbon in the atmosphere, with average measured levels ranging from 0.14 to 59 µg/liter (USEPA, 1983). Toluene has been detected in surface water and in treated wastewater effluents at levels generally below 10 µg/liter. A concentration of toluene as high as 19 µg/liter has been detected in a drinking water supply. In a study of toluene levels in the tissue of edible aquatic organisms, 95% of the samples contained less than 1 ppm of toluene.

HUMAN EXPOSURE

The estimated intake of toluene by the general public is between a trace and 94 mg per week by inhalation (depending on whether an individual resides in an urban or rural area or near an industry that uses toluene) and 0-0.75 mg per week from food and water (USEPA, 1983). Occupational exposure (up to 18,000 mg per week) or cigarette smoking (0.1 mg per cigarette) adds considerably to an individual's exposure to toluene. Exposure also occurs through deliberate inhalation of solvents found in various preparations, such as glue (sniffing). An estimated 124 million people in the United States are exposed to atmospheric toluene at a concentration greater than 0.27 µg/liter.

METABOLISM

The metabolism of toluene has been extensively reviewed (IPCS, 1985; CTFA, 1986; Wallen, 1986; USEPA, 1987). Toluene is readily absorbed from the respiratory tract of mammals (Nomiyama and Nomiyama, 1974; Sato et al., 1974a,b; Astrand, 1975; Egle and Gochberg, 1976; Sherwood, 1976; Carlsson and Lindqvist, 1977; Sato and Nakajima, 1979; Benignus, 1981a; WHO, 1981; Carlsson, 1982; Rees et al., 1985). In humans, the uptake of toluene is 40%-60% of the amount inhaled (Nomiyama and Nomiyama, 1974). The uptake of toluene through the skin of humans (with respiratory protection) exposed at 600 ppm in air for 3.5 hours was 1% of the theoretical respiratory uptake; the toluene concentration in peripheral venous blood after 1, 2, and 3 hours of exposure was approximately 100 µg/liter (Riihimaki and Pfaffli, 1978). Toluene is almost completely absorbed from the gastrointestinal tract (Smith et al., 1954; El Masry et al., 1956; Cohr and Stokholm, 1979; Syracuse Research Corp., 1983; Slooff and Blokzijl, 1988).

In mice exposed to toluene at 4,000 ppm for 3 hours, the concentration of toluene was 625 mg/kg in liver, 420 mg/kg in brain, and 200 mg/kg in blood (Peterson and Bruckner, 1978; Bruckner and Peterson, 1981a). Immediately after adult male rats were exposed to [methyl-^{14}C]toluene at 550 ppm by inhalation for 1 hour, the amount of radioactive label in adipose tissue was more than two times the amount in any other organ (Carlsson and Lindqvist, 1977). Six hours after exposure, radioactivity was still measurable in liver, kidney, and adipose tissue. In studies with mice exposed to [methyl-^{14}C]toluene by inhalation, high levels of radioactive label were found in adipose tissue, bone marrow, spinal nerves, spinal cord, and white matter of brain (Bergman, 1979, 1983). Radioactivity was no longer detectable in nervous system tissue 1 hour after exposure and was cleared from body fat after 4 hours. Traces of nonvolatile radioactivity were present after 4 hours, but no radioactivity was detectable by 24 hours. Distribution of toluene to tissues after gavage administration is similar to, but slower than, that after inhalation exposure (Pyykko et al., 1977). Studies in adult male Wistar rats exposed to toluene at 300 ppm (6 hours per day for 1-15 weeks) indicated a decrease of toluene in perirenal fat over time, suggesting enhanced activity of drug-metabolizing enzymes in liver and metabolic and functional adaptation after long-term low-level exposure (Elovaara et al., 1979).

After an intraperitoneal injection of [methyl-^{14}C]toluene at 500 μmol to rats, the concentration of radioactivity was highest in the cerebrum (Savolainen, 1978). After an intraperitoneal injection at 0.2 mg/kg to mice, most of the radioactivity in the adipose tissue and brain was volatile (probably unmetabolized toluene), whereas most of the radioactivity in the liver and kidney was nonvolatile (probably a metabolite) (Koga, 1978).

When pregnant CFY rats were exposed to toluene at 370 or 720 ppm for 24 hours on days 10-13 of gestation, the toluene concentration 2 hours after exposure was 6.4 or 1 3.7 mg/liter in maternal blood and 4.9 or 10.4 mg/liter in fetal blood (Ungvary, 1984).

Toluene is rapidly metabolized primarily in the liver (SRI, 1980; Slooff and Blokzijl, 1988). In rats, rabbits, and humans, 25%-40% of an oral or inhaled dose is excreted unchanged in exhaled air, and 60%-75% of the dose is converted to benzoic acid and excreted in urine, primarily as hippuric acid; smaller amounts are excreted as the sulfate or glucuronide conjugate of benzoic acid (Figure 1) (von Oettingen et al., 1942a; Srbova and Teisinger, 1952; Smith et al., 1954; El Masry et al., 1956; Daly et al., 1968; Bakke and Scheline, 1970; Angerer, 1976; Pfaffli et al., 1979; Toftgard and Gustafsson, 1980; Van Doorn et al., 1980; Woiwode and Drysch, 1981; Baelum et al., 1987). Less than 1% of the absorbed toluene is hydroxylated to *o*-, *m*-, or *p*-cresol, which is then excreted as the sulfate or glucuronide conjugates (DeBruin, 1976; Woiwode et al., 1979; Baelum et al., 1987). The first step in the conversion of toluene to benzoic acid is conversion to benzyl alcohol by an NADH-dependent hydratase or a monooxygenase (Bakke and Scheline, 1970; SRI, 1980). The benzyl alcohol is rapidly converted to benzaldehyde by an NAD-dependent alcohol dehydrogenase, and the benzaldehyde is converted to benzoic acid by an NAD-dependent aldehyde dehydrogenase (SRI, 1980; IPCS, 1985). *o*-Cresol or hippuric acid in the urine is an indication of toluene exposure in workers (Angerer, 1979; Ogata et al., 1970; Woiwode and Drysch, 1981; Apostoli et al., 1982; Andersson et al., 1983; Dossing et al., 1983; Hasegawa et al., 1983; Kono et al., 1985; De Rosa et al., 1985, 1986, 1987; Ogata and Taguchi, 1986); however, Baelum et al. (1985a) indicated that urinary *o*-cresol concentrations give a more specific estimate of toluene exposure than hippuric acid concentrations. *o*-Cresol excretion is delayed compared with hippuric acid excretion and is more consistent when exposure is accompanied by physical activity (Baelum et al., 1987). In rats exposed to toluene at 5-500 ppm by inhalation, the urinary ratio of hippuric acid to *o*-cresol was constant, but at 2,500 or 3,500 ppm, the amount of *o*-cresol increased sharply (Inoue et al., 1984). Of four strains of rats exposed to toluene, F344 rats excreted the most *o*-cresol and Sprague Dawley rats excreted the least; Wistar

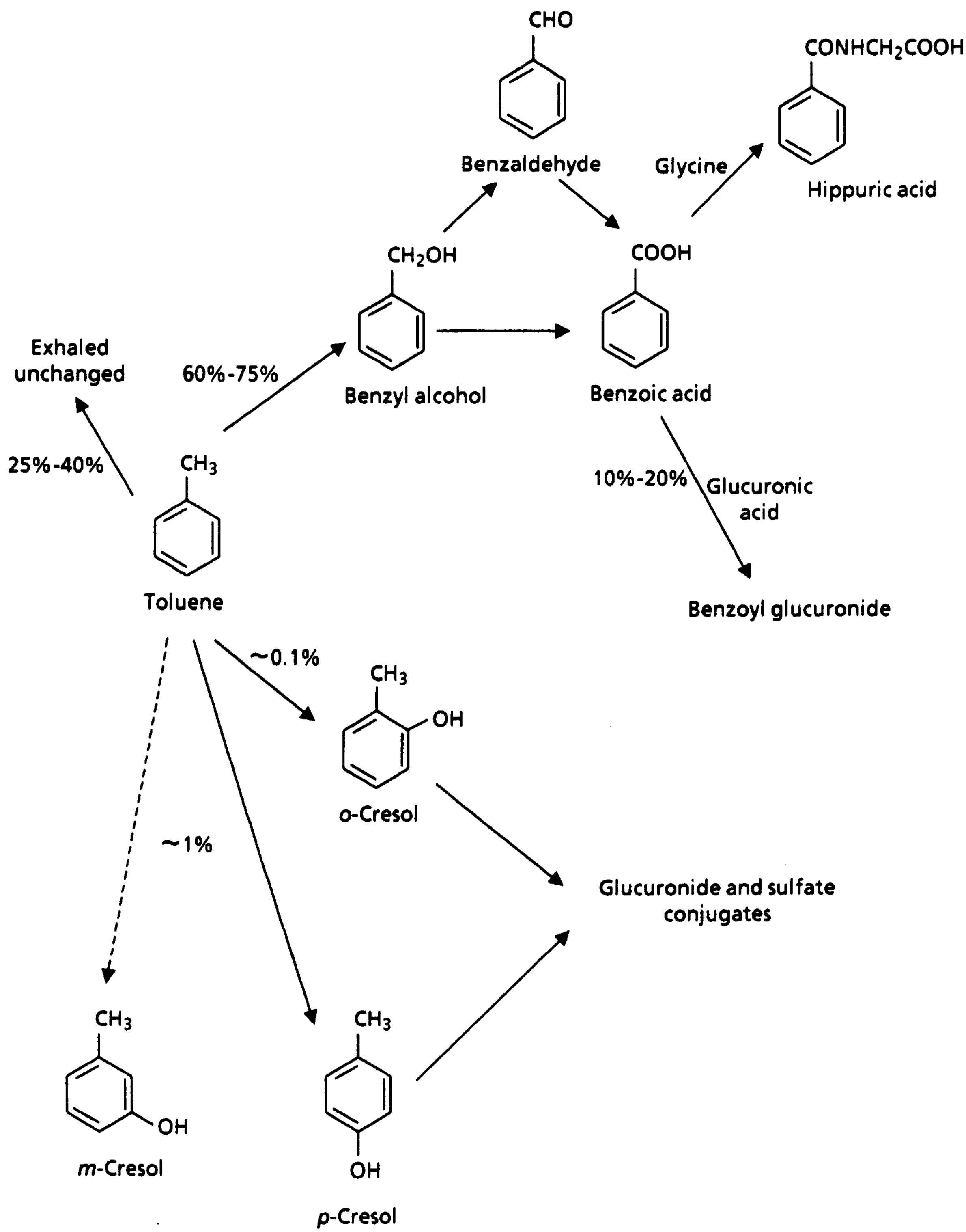


FIGURE 1. METABOLISM OF TOLUENE IN HUMANS AND ANIMALS
(taken from IPCS, 1985, and modified)

rats excreted the most *p*-cresol. A biologic exposure index based on the direct analysis of toluene in urine has been suggested by Pezzagno et al. (1985), who found a correlation between the concentration of toluene in air and in urine.

TOXICITY IN ANIMALS

Extensive reviews of the toxicity of toluene are presented in the International Programme on Chemical Safety (IPCS, 1985), Cosmetic, Toiletry and Fragrance Association (CTFA, 1986), Bell et al. (1988), Agency for Toxic Substances and Disease Registry (ATSDR, 1989), and International Agency for Research on Cancer (IARC, 1989).

Short-Term Studies

Oral LD_{50} values for toluene range from 2.6 to 7.5 g/kg for juvenile to adult rats (Cameron et al., 1938; Kimura et al., 1971; Withey and Hall, 1975; Ungvary et al., 1979). The dermal LD_{50} is 14.1 ml/kg for rabbits (Smyth et al., 1969). The LC_{50} value for a 6- to 7-hour exposure is 12,200 ppm for rats (Cameron et al., 1938) and 5,300-7,000 ppm for mice (Svirbely et al., 1943; Bonnet et al., 1979). The intraperitoneal LD_{50} is 1.64 g/kg for female rats (Ikeda and Ohtsuji, 1971). In freshwater organisms, the LC_{50} for mosquito larvae is 21.5 mg/liter, whereas for fathead minnows, the LC_{50} is 26 mg/liter for juveniles and 29 mg/liter for day-old fry. The LC_{50} values for marine organisms include 3.7 mg/liter for bay shrimp and 28 mg/liter for Dungeness crabs (Caldwell et al., 1976; Benville and Korn, 1977; Berry and Brammer, 1977; USEPA, 1980; Devlin et al., 1982).

Adverse effects were observed in animals administered toluene by various routes of exposure. Undiluted toluene was found to be an ocular and skin irritant (Wolf et al., 1956; Guillot et al., 1982a,b). Slight induration at the injection site, decreased body weight, hyperplasia of bone marrow and of malpighian corpuscles in the spleen, marked pigmentation of spleen, focal necrosis of the liver, and slight cloudy swelling in the kidney were seen in rats given subcutaneous injections of toluene at 1 ml/kg for 21 days (Batchelor, 1927). In guinea pigs, toluene given by subcutaneous injection at 0.25 ml per day for 30-70 days caused necrosis at the injection site, polypnea and convulsions toward the end of the studies, and hemorrhagic, hyperemic, and degenerative changes in the lung, kidney, adrenal gland, liver, and spleen (Sessa, 1948). An increased number of casts was seen in the collecting tubules of the kidney in rats exposed to toluene (99.9% pure) in air at 200-5,000 ppm, 7 hours per day, 5 days per week for 5 or 15 weeks, and in dogs exposed at 200-600 ppm, 8 hours per day for 20 days, followed by exposure for 7 hours per day, 5 days per week for 1 week, and then at 850 ppm for 1 hour (von Oettingen et al., 1942a).

Toluene at near lethal exposure concentrations (up to 66,000 ppm for up to 30 minutes) had no untoward electrocardiographic effects and even appeared to decrease epinephrine-induced ectopic beats in male Wistar rats (220-242 g) (Vidrio et al., 1986).

Six-Month to One-Year Studies

DONRYU male rats were exposed to 0, 100, 200, or 2,000 ppm toluene vapor 8 hours per day, 6 days per week, for 10, 18, or 43 weeks (Matsumoto et al., 1971). The most significant histopathologic change was in the kidney; numerous eosinophilic droplets of various sizes (termed by the authors as "hyaline droplets") were observed in the renal tubular epithelium in each exposed group. Only a few droplets were seen in controls. The longer the duration, the larger and more frequent were the hyaline droplets. In the 2,000-ppm toluene group exposed for 43 weeks, the droplets were large and the amounts were increased. Matsumoto and coworkers indicated that the hyaline droplets originated from degenerated microsomes, and although the droplets were seen after proteinuria was evident, the relationship between hyaline droplets and proteinuria was not examined. [Note: In January 1989, at NTP's request, Dr. Matsumoto kindly sent several Kodachrome slides of the kidney sections from his 1971 study; these were examined, and the typical hyaline droplet nephropathy was not observed.]

No histopathologic effects were seen in female Wistar rats after gavage administration of toluene in olive oil and gum arabic at 590 mg/kg, 5 days per week for 6 months (Wolf et al., 1956); in

Sprague Dawley rats after inhalation exposure at 1,481 ppm, 6 hours per day, 5 days per week for 6 months (API, 1980); or in OFA rats after inhalation exposure at 1,000 ppm, 6 hours per day, 5 days per week for 6 months (Gradiski et al., 1981).

Hematologic Effects

Leukocytosis, decreased thrombocyte and erythrocyte counts, and bone marrow hypoplasia were observed for mice exposed to toluene (grade unspecified) by inhalation at 1,000 ppm for 20 days or at 4,000 ppm for 8 weeks (Horiguchi and Inoue, 1977; Bruckner and Peterson, 1981b). A transient, slight granulopenia followed by granulocytosis was seen in rabbits administered toluene (grade unspecified) by gavage at 865 mg/kg for 6 days (Braier, 1973). These effects may have been due to the presence of benzene as a contaminant (percent not reported) in the toluene (USEPA, 1987).

No effect on hematologic values was reported for rats exposed to toluene by inhalation at 1,000 ppm for 6 weeks (Jenkins et al., 1970; Bruckner and Peterson, 1981b) or Sprague Dawley rats exposed to toluene by inhalation at 1,000 ppm, 8 hours per day, 7 days per week for 13 weeks (Tahti et al., 1983). No effect on hemoglobin concentration, hematocrit, or leukocyte count was observed for rats, guinea pigs, dogs, or monkeys exposed to toluene by inhalation continuously at 103 ppm or at 1,092 ppm for 8 hours per day, 5 days per week for 6 weeks (Jenkins et al., 1970). No hematologic effects were seen in female Wistar rats after gavage administration of toluene in olive oil and gum arabic at 590 mg/kg, 5 days per week for 6 months (Wolf et al., 1956); in Sprague Dawley rats after inhalation exposure at 1,481 ppm, 6 hours per day, 5 days per week for 6 months (API, 1980); in OFA rats at 1,000 ppm, 6 hours per day, 5 days per week for 6 months (Gradiski et al., 1981); or in F344 rats at 299 ppm, 6 hours per day, 5 days per week for 24 months (Gibson and Hardisty, 1983).

Central Nervous System Effects

The brain is highly vascularized and has a high lipid content. Therefore, the high lipid solubility of toluene indicates the possibility of a wide distribution in the brain following exposure (Benignus, 1981a). The initial uptake of toluene (after a 10-minute inhalation exposure) was greatest in the medulla/pons, followed by midbrain, cerebellum, thalamus, frontal cortex, hippocampus, caudate, and hypothalamus (Gospe and Calaban, 1988). The toluene uptake correlated with the total lipid content of each brain region. In spite of the clinical and epidemiologic data implicating toluene as a neurotoxicant, there are few studies that have systematically studied this problem in animals.

The central nervous system response to toluene is biphasic--an initial excitable phase followed by central nervous system depression (Contreras et al., 1979). At vapor concentrations less than 2,000 ppm or exposure for less than 30 minutes, increased locomotor activity in rats (Yamawaki and Sarai, 1982), operant response rates in rats and mice (Weiss et al., 1979; Glowa, 1981; Moser and Balster, 1981, 1985; Wood et al., 1983; Bushnell et al., 1985), and sensitivity to shock and heat in rats (Contreras and Bowman, 1982) were generally observed. Exposure to toluene at concentrations higher than 2,000 ppm suppressed activity (Cohr and Stokholm, 1979; Moser and Balster, 1981). Exposure of rats to toluene at 1,000 ppm produced excitability, followed by depression of cortical activity which resulted in coma (Contreras et al., 1979). Brief inhalation exposure at 3,500-4,500 ppm for 50 minutes impaired the cognitive and motor abilities in macaque monkeys (Taylor and Evans, 1985). In rats, Ikeda and Miyake (1978) reported impaired learning after repeated toluene exposure at 4,000 ppm, 2 hours per day for 60 days.

Hearing loss was reported for rats exposed to toluene at 7,550 mg/m^3 for 8 hours per day for 3 days or 5,660 mg/m^3 for 14 hours per day as weanlings or as young adults (Pryor et al., 1984). Toluene given to F344 and Sprague Dawley rats at 620 mg/kg by gavage once per day for 4 weeks was shown to produce hearing loss by damaging the outer hair cells of the inner ear (Sullivan, 1986). Continuous inhalation exposure of male Sprague Dawley rats to toluene at 320 ppm resulted in decreased weight of the whole brain and the cerebral cortex; the phospholipid content of the cerebral cortex was significantly decreased (Kyrklund et al., 1987).

Pryor et al. (1983a) examined the effects of 14-week inhalation exposure of weanling rats to toluene and found that toluene had no consistent effect on measures of forelimb and hind limb grip strength, motor activity, startle reactivity (acoustic or air-puff stimuli), or reactivity to a thermal stimulus. *n*-Hexane, a known neurotoxicant, had marked effects on neuromuscular components of this neurobehavioral test battery. However, toluene-exposed rats were found to acquire a multisensory conditional avoidance response more slowly than controls and had an altered component of the brainstem auditory-evoked response. Toluene-exposed animals were also tested in a tone-intensity discrimination task and found to be deficient. In a subsequent study, Pryor et al. (1983b) reported that weanling rats exposed to toluene were impaired in learning a conditioned avoidance response if the conditioning stimulus was a 20-kHz tone; learning was not affected by toluene exposure if the training cue was visual or somatosensory. These behavioral measurements were made during the course of repeated toluene exposure. In subsequent studies, rats were tested 2.5 months after cessation of exposure; hearing of toluene-exposed animals was unimpaired at 4 kHz, slightly impaired at 8 kHz, and markedly impaired at 12 kHz or above. Rebert et al. (1983), using electrophysiologic techniques, examined the auditory effects of toluene 2.5 months after cessation of exposure; the thresholds for brainstem auditory-evoked responses were increased twofold, and the latency-intensity functions were consistent with the occurrence of sensory loss, i.e., ototoxicity. Therefore, unlike solvents such as *n*-hexane, there is little evidence that toluene produces peripheral neuropathy. However, if exposure occurs repeatedly in young animals, toluene produces behavioral and electrophysiologic alterations indicating toxicity.

Fetotoxicity and Teratogenicity

Skeletal anomalies were observed in the fetuses of rats and mice exposed to toluene by inhalation or gavage during gestation at doses that were not toxic to the dams. Cleft palates were seen in the fetuses of CD®-1 mice given 1 ml/kg (870 mg/kg) toluene in cottonseed oil by gavage on days 6-15 of gestation (Nawrot and Staples, 1979). At this dose, an increase in embryonic deaths and reduced fetal weights were also observed. An increase in irregular sternebrae or extra fused ribs was seen in the fetuses of CFY rats continuously exposed to toluene at 400 ppm by inhalation on days 9-14 of gestation (Hudak and Ungvary, 1978). An increase in rudimentary 14th ribs or in extra ribs was seen in the fetuses of ICR mice exposed to toluene at 1,000 ppm by inhalation for 6 hours per day on days 1-17 of gestation (Shigeta et al., 1981, 1982) and in the fetuses of CFY rats exposed to toluene at 266 ppm by inhalation for 24 hours per day on days 7-14 of gestation (Tatrai et al., 1980) or exposed at 1,000 pm for 24 hours per day on days 7-15 (Ungvary, 1985). A significant increase in the number of fetuses with 13 ribs was observed for CD®-1 mice exposed to pesticide-grade toluene at 400 ppm by inhalation for 7 hours per day on days 6-16 of gestation (Courtney et al., 1986). Decreased weights, but no malformations, were observed for the fetuses of CFLP mice continuously exposed to toluene at 133 ppm by inhalation on days 6-13 of gestation (Hudak and Ungvary, 1978). Retarded bone ossification and inhibition of growth, but no teratogenic effects, were observed for the fetuses of Charles River rats exposed to toluene (99.96% pure) at 400 ppm by inhalation for 6 hours per day on days 6-15 of gestation (LBI, 1978a). Deaths, but no teratogenic effects, were observed for the fetuses of New Zealand rabbits continuously exposed to toluene at 266 ppm by inhalation on days 6-20 of gestation (Ungvary and Tatrai, 1985).

Genetic Toxicology

Toluene has been studied extensively for genotoxic effects both in vitro and in vivo, and the overwhelming weight of evidence indicates that the chemical is not genotoxic. A summary of these results is presented in Table 1. The positive responses reported in in vivo studies may have resulted from artifacts of the protocol or possibly from contaminants in the toluene samples. For example, the detection of single-strand breaks reported by Sina et al. (1983) was probably a secondary effect of cell lysis rather than direct interaction of toluene with nuclear DNA because it occurred only when cytotoxicity was greater than 30%. The studies reporting induction of chromosomal aberrations by toluene

TABLE 1. SUMMARY OF THE GENETIC TOXICOLOGY STUDIES OF TOLUENE

Test System/Reference	Endpoint	Dose	Results
Bacteria			
Bacillus subtilis			
McCarroll et al., 1981a	Growth inhibition due to DNA damage		Negative
Escherichia coli			
Fluck et al., 1976	Growth inhibition due to DNA damage	25 µl/plate	Negative
McCarroll et al., 1981b	Growth inhibition due to DNA damage		Negative
Mortelmans and Riccio, 1980	Gene mutation	0.01-10 µl/plate	Negative
Salmonella typhimurium			
Mortelmans and Riccio, 1980	Growth inhibition due to DNA damage	0.001-0.01 µl/plate	Negative
	Gene mutation	0.01-10 µl/plate	Negative
Anderson and Styles, 1978	Gene mutation		Negative
LBI, 1978b	Gene mutation	0.001-5 µl/plate	Negative
Nestmann et al., 1980	Gene mutation		Negative
Florin et al., 1980	Gene mutation	0.03-30 µmol/plate	Negative
Snow et al., 1981	Gene mutation	0.3-100 µl/plate	Negative
Bos et al., 1981	Gene mutation	0-2,000 µg/plate	Negative
Spanggord et al., 1982	Gene mutation	0-5 mg/plate	Negative
Haworth et al., 1983	Gene mutation	0-1,000 µg/plate	Negative
Yeast			
Saccharomyces cerevisiae			
LBI, 1978b	Mitotic gene conversion	0.001-5 µl/plate	Negative
Mortelmans and Riccio, 1980	Mitotic gene conversion	0.001%-5%	Negative
	Mitotic crossing over	0.001%-5%	Negative
	Gene mutation	0.001%-5%	Negative
Mammalian Cells in Vitro			
Mouse lymphoma L5178Y cells			
LBI, 1978b	Trifluorothymidine resistance	0-0.3 µl/ml	Negative
McGregor et al., 1988	Trifluorothymidine resistance	6.25-500 µg/ml	Equivocal
Chinese hamster ovary cells			
Evans and Mitchell, 1980	Sister chromatid exchange	0.0025%-0.04%, 21.4 h	Negative
	Sister chromatid exchange	0.0125%-0.21%, 2 h	Negative
Human lymphocytes			
Gerner-Smidt and Friedrich, 1978	Sister chromatid exchange	0-1,520 µg/ml	Negative
Mammalian Cells in Vivo			
Rat			
Dobrokhotov, 1972	Chromosomal aberrations	0.8 g/kg/d for 12 d	(a) Positive
Lyapkalo, 1973	Chromosomal aberrations	1 g/kg/d for 12 d	(a) Positive
Dobrokhotov and Enikeev, 1975	Chromosomal aberrations	80 ppm, 4 h/d for 4 mo	(a) Positive
LBI, 1978b	Chromosomal aberrations	0-214 mg/kg	Negative
Sina et al., 1983	DNA single-strand breaks	0-3 mM	(b) Positive
Mouse			
Kirkhart, 1980	Micronucleus induction	0-1,000 mg/kg	Negative
Topham, 1980	Sperm head abnormalities	0-1.5 mg/kg/d	Negative
LBI, 1981	Dominant lethal mutations	400 ppm, 6 h/d, 5 d/wk for 8 wk	Negative
Tice et al., 1982	Sister chromatid exchange	0-32.4 mmol/kg	Negative
Gad-El-Karim et al., 1984	Micronucleus induction	860-1,720 mg/kg	Negative
	Chromosomal aberrations	860-1,720 mg/kg	Negative

(a) Purity of chemical unspecified; possible contamination with benzene.
(b) Greater than 30% cell lethality

(Dobrokhotov, 1972; Lyapkalo, 1973; Dobrokhotov and Enikeev, 1975) were difficult to evaluate because the types of aberrations scored were unclear, cells scored from a group of animals were pooled rather than analyzed individually, and, in one case (Dobrokhotov and Enikeev, 1975), there was no indication of the numbers of cells actually scored. Further, none of these positive studies specified the purity of the toluene sample used. Since nonreagent-grade toluene is frequently contaminated with varying amounts of benzene, it is possible that the increased incidence of chromosomal aberrations reported was due to exposure to benzene, a demonstrated in vivo clastogen. Similar contamination of toluene samples (purity unspecified) evaluated in other in vitro assays (e.g., for mutation induction in bacteria) would not be expected to give positive responses because benzene is negative in these assays (NTP, 1986a; Huff et al., 1989).

Several investigators have examined toluene-exposed factory workers for cytogenetic effects (Forni et al., 1971; Funes-Cravioto et al., 1977; Maki-Paakkanen et al., 1980; Bauchinger et al., 1982). The studies that reported increased levels of chromosomal aberrations or sister chromatid exchanges (SCEs) in exposed workers compared with unexposed populations failed either to adequately document that chemical exposure was to toluene alone (Funes-Cravioto et al., 1977) or to consider the data from smokers separately from those from nonsmokers (Bauchinger et al., 1982). When Bauchinger et al. (1982) reanalyzed the SCE data according to the smoking history of the workers, they still reported a small but significant increase in SCEs in the toluene-exposed groups; however, a similar reanalysis of the chromosomal aberration data (Integrated Criteria Document Toluene) eliminated the reported difference between exposed and nonexposed workers.

The metabolites of toluene for which there are data available are also nongenotoxic. Benzyl alcohol (NTP, 1989a) was negative in bacterial assays for induction of DNA damage (Fluck et al., 1976; Oda et al., 1978) or gene mutation (Florin et al., 1980; Mortelmans et al., 1986) and did not cause DNA single-strand breaks or chromosomal aberrations in human fibroblasts in vitro (Waters et al., 1982). Benzoic acid was negative in assays for induction of gene mutation in Salmonella (McCann et al., 1975; Anderson and Styles, 1978; Simmon and Kauhanen, 1978; Zeiger et al., 1988), mitotic recombination in yeast (Simmon and Kauhanen, 1978), SCEs in Chinese hamster ovary cells (Oikawa et al., 1980), and SCEs and chromosomal aberrations in cultured human fibroblasts (Tohda et al., 1980; Zhurkov, 1975). Hippuric acid was negative in Salmonella gene mutation assays (Milvy and Garro, 1976; Wiessler et al., 1983). The cresols (*m*- and *p*-) were negative for induction of gene mutation in Salmonella (Pool and Lin, 1982; Haworth et al., 1983) and did not induce SCEs in human fibroblasts in vitro or in mouse fibroblasts in vivo (Cheng and Kligerman, 1984). The genotoxicity profile for *o*-cresol was similar, with the exception of a weakly positive response in the in vitro SCE assay with human fibroblasts in which a significant increase in SCEs was observed at the highest nontoxic dose tested (Cheng and Kligerman, 1984).

Carcinogenicity

A summary of the dermal, gavage, and inhalation carcinogenicity studies with toluene which have been reported in the literature is available (CTFA, 1986; Bell et al., 1988; IARC, 1989). Results for carcinogenicity were uniformly negative, although Lijinsky and Garcia (1972) reported on the occurrence of one papilloma in 30 mice exposed to 16-20 µl toluene (as toluene vehicle controls) by topical application two times per week for 72 weeks and one carcinoma in another mouse; none occurred in the acetone vehicle controls. Toluene was used as a vehicle in numerous dermal initiation/promotion studies in mice (Poel, 1963; Frei and Stephens, 1968; Lijinsky and Garcia, 1972; Vose et al., 1981; Blackburn et al., 1984), directly in dermal application studies (Coombs et al., 1973; Doak et al., 1976; Coombs and Bhatt, 1978), and in a 3-month subcutaneous implant study (Purchase and Longstaff, 1978). Application of 40 µl toluene two times per week at the initiation/promotion site on the back reduced the average number of skin tumors per mouse at week 15 for C3H mice initiated with 1 mg benzo[*a*]pyrene or for CD®-1 mice initiated with 2.5 µg dimethylbenz[*a*]anthracene followed by promotion with

1-5 μg phorbol-12-myristate-13-acetate two times per week (Weiss et al., 1986).

At week 92, the incidences of neoplasms seen at various sites were not compound related in groups of 40 male and 40 female Sprague Dawley rats given 500 mg/kg toluene (98.3% pure) in olive oil by gavage 4-5 days per week for 2 years (Maltoni et al., 1983). At the end of the study (week 141), hemolymphoreticular neoplasms were reported in 3/37 toluene-exposed males and 7/40 toluene-exposed females compared with 3/45 and 1/49 in vehicle controls (Maltoni et al., 1985). Also reported were the numbers of animals with malignant tumors (olive oil control male, 11/45 vs. toluene-exposed male, 18/40; female, 10/49 vs. 21/40) and the total number of malignancies per group (male, 12/45 vs. 23/40; female, 11/49 vs. 32/40). In another inhalation study using F344 rats (Gibson and Hardisty, 1983), the incidences of neoplasms in groups of 120 male and 120 female F344 rats exposed to air containing toluene at 0, 30, 100, or 300 ppm, 6 hours per day, 5 days per week for 2 years, were not significantly different from those in controls.

Several metabolites of toluene have been or are being evaluated in long-term studies in rodents. No evidence of carcinogenicity of benzyl alcohol was seen in male or female F344/N rats given 0, 200, or 400 mg benzyl alcohol/kg body weight 5 days per week in corn oil for 2 years (NTP, 1989a). At one-half these doses, no evidence of carcinogenicity was found in male or female $B6C3F_1$ mice. To study the effects of antioxidants on BHA-induced forestomach carcinogenesis, Ito exposed groups of 15 F344 rats to 2% benzoic acid in the diet for 52 weeks with and without 2% butylated hydroxyanisole (BHA) (IARC, 1988a; personal communication from N. Ito, Nagoya City University Medical School, to J. Huff, NTP, December 1988). Benzoic acid did not modify the incidences of BHA-induced forestomach neoplasms, and benzoic acid alone did not cause forestomach hyperplasia. Long-term studies of benzaldehyde are currently being evaluated (NTP, 1989b). F344/N rats and male $B6C3F_1$ mice were given 0, 200, or 400 mg benzaldehyde/kg body weight in corn oil by gavage, and female mice were given 0, 300, or 600 mg/kg. Short-term studies have been completed on *o*-cresol and mixed *m*- and *p*-cresols (personal communication from D. Dietz, NTP, 1989).

TOXICITY IN HUMANS

Central Nervous System Effects

Inhalation of toluene produces symptoms of nervous system dysfunction and signs of neurologic impairment (Longley et al., 1967; Benignus, 1981a), which appear to be reversible except for long-term abusers (Benignus, 1981b). After a single exposure to toluene at 50-1,500 ppm for 3-8 hours, individuals developed fatigue, drowsiness, impaired cognitive function, incoordination, and irritation of the eyes and throat; these effects increased in severity with increases in concentration and progressed to pronounced nausea, staggering gait, confusion, extreme nervousness, muscular fatigue, and insomnia lasting for several days (Ogata et al., 1970; Gamberale and Hultengren, 1972; Carpenter et al., 1976; Winneke, 1982; IPCS, 1985; Baelum et al., 1985b). Narcosis increased after exposure at 4,000-30,000 ppm, with death occurring after exposure at the highest concentrations for from a few minutes to greater than 1 hour (von Oettingen, 1942a,b; IPCS, 1985). Long-term toluene abusers (for at least 1 year) reported disturbed behavior; slow thought and speech; illusionary misinterpretations; tactile, auditory, and visual hallucinations; and delusional ideas (Evans and Raistrick, 1987). Cerebellar dysfunction, mental retardation, abnormal electroencephalograms, brain atrophy, and visual impairment were observed in long-term (6-14 years) abusers of pure toluene (Grabski, 1961; Knox and Nelson, 1966; Sasa et al., 1978; Malm and Lying-Tunnell, 1980; Lewis et al., 1981; Takeuchi et al., 1981; Lazar et al., 1983). Juntunen et al. (1985) reported that long-term occupational exposure (up to 22 years) of 43 male rotogravure printers at an estimated 117 ppm toluene had no clinically significant adverse effects on the nervous system.

Kidney and Liver Effects

Effects of toluene abuse on the kidney (pyuria, hematuria, and proteinuria) have been summarized (IPCS, 1985; USEPA, 1987). Most of the persons with symptoms or signs of toluene sniffing were also exposed to other solvents. Renal tubule effects, indicated by metabolic acidosis (hypokalemia, hypophosphatemia, and hyperchloremia), have been associated with abusers of toluene-containing solvents (Sokol and Robinson, 1963; Taher et al., 1974; Fischman and Oster, 1979; Bennett and Forman, 1980; Kroeger et al., 1980; Moss et al., 1980; Voigts and Kaufman, 1983; Patel and Benjamin, 1986); the contribution of toluene to these effects is not clear. Nielsen et al. (1985) and Krusell et al. (1985) claim that no causal relationship exists between exposure to toluene alone and renal injury (as measured by excretion of albumin and $\beta_{2\mu}$-globulin). In contrast, increased protein excretion and increased excretion of erythrocytes and leukocytes/tubular epithelial cells were reported for construction workers exposed to toluene (Askergren, 1984). A positive relationship exists between alcohol consumption before exposure to toluene and the urinary excretion rate of albumin (Krusell et al., 1985). Hepatomegaly was noted for 61 airplane painters exposed to toluene at 100-1,115 ppm in air for up to 5 years (Greenberg et al., 1942). In another study, hepatomegaly was observed for 20%-50% of workers exposed to toluene at 53-80 ppm in air for 2-14 years, but biopsies from 22 of the workers indicated no pathologic changes in liver (Szilard et al., 1978). Liver impairment was observed in long-term (6-14 years) abusers of pure toluene (Grabski, 1961; Knox and Nelson, 1966; Takeuchi et al., 1981).

Hematologic Effects

Early reports (generally pre-1950) of occupational exposure ascribed myelotoxic effects to toluene (Ferguson et al., 1933; Greenberg et al., 1942; Wilson, 1943), but most of the recent evidence indicates that toluene does not cause toxic effects in blood or bone marrow (Parmeggiani and Sassi, 1954; Capellini and Alessio, 1971; Matsushita et al., 1975; Tahti et al., 1981; Yin et al., 1987). Eosinophilia, leukocytosis, low hemoglobin concentration, basophilic stippling of erythrocytes, and poikilocytosis, anisocytosis, hypochromia, and polychromasia were observed for sniffers of toluene-based glues (Sokol and Robinson, 1963). Myelotoxic effects previously attributed to toluene are currently considered to have been the result of concurrent exposure to benzene, typically present as a contaminant in commercially available toluene (USEPA, 1987).

Teratogenicity

No studies linking toluene and birth defects have been reported. All studies or reports were of solvent mixtures containing toluene (Euler, 1967; Syrovadko, 1977; Holmberg, 1979; Hersh et al., 1985).

Carcinogenicity

No published epidemiology studies on toluene were located. At least two studies are underway: one in Sweden and one in the United States (IARC, 1988b). Several epidemiology studies in which workers were exposed to other solvents as well as to toluene are described in IARC (1989).

STUDY RATIONALE

The aromatic six-member hydrocarbon (benzene), the monomethyl derivative (toluene), and the dimethyl derivatives (xylenes) were nominated and selected for toxicology and carcinogenesis characterization because each met several of the eight criteria of the Chemical Selection Principles established by the National Toxicology Program in 1978. These include considerable production volume, widespread occupational and general population exposure, and lack of adequate long-term studies at the time these chemicals were selected and the studies designed. Additionally, long-term studies on these three chemicals would provide some indications of structure-activity associations for benzene and simple alkylbenzenes. For toluene, the short-term studies were conducted using both the gavage and inhalation routes of exposure so that the two routes could be compared. The 2-year studies used inhalation exposure to better mimic human occupational exposure (although oral and dermal exposure also occur) and to compare the results with those from an earlier study by Gibson and Hardisty (1983).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF TOLUENE

Toluene was obtained in one lot (lot no. H-12-19-80) from Exxon Company, USA (Baytown, TX) as a clear, colorless liquid and was received in sixteen 55-gallon drums. Purity and identity analyses were conducted on representative samples at Midwest Research Institute (Kansas City, MO) (Appendix I). The study material was identified as toluene by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

The toluene study material was found to be greater than 99% pure, as determined by elemental analysis, Karl Fischer water analysis, and gas chromatography. Gas chromatography by two systems detected three impurities with individual peak areas less than 0.1% of the major peak area. Benzene content of the study material was determined by spiking with benzene and then quantitating against a benzene reference standard and was found by gas chromatography to be present as an impurity at a concentration of 5.7 ppm (v/v). (The calculated benzene concentrations used in these studies were 0.82, 4.1, and 8.2 ppb for the toluene exposures at 120, 600, or 1,200 ppm.)

Periodic analysis of the toluene for purity by gas chromatography and ultraviolet spectroscopy and for identity by infrared spectroscopy indicated no apparent degradation of the study material throughout the studies.

CHARACTERIZATION OF DOSE MIXTURES

Toluene dissolved in corn oil at 20 mg/ml was found to be stable for at least 2 weeks when stored protected from air and light at 5° C and at room temperature. Solutions exposed to air and light for 3 hours were chemically stable, but a 23% loss due to evaporation was observed over the 3-hour period. Dose mixtures were stored at room temperature protected from light in Nalgene® bottles for no longer than 2 weeks throughout the studies. Dose mixtures were analyzed several times during the 13-week studies and found to be within ±10% of the target concentrations.

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

Vapor Generation System

Toluene vapor was generated by delivering liquid toluene to a heated Spraying Systems® atomizer that was operated with nitrogen (Appendix I). Toluene vapor was diluted with chamber ventilation air to produce the desired exposure concentrations in the chambers. The uniformity of the vapor concentrations in each exposure chamber was measured several times during the studies. Generally good chamber distribution of the toluene vapor was observed in these studies.

Vapor Concentration Monitoring

The concentration of toluene in the chambers was measured in sampled chamber air at 3.3 μ by a MIRAN® gas-phase infrared spectrophotometer connected to a Hewlett-Packard Model 3388A laboratory computer. Air from each chamber was sampled and analyzed about 5 minutes every hour. Data were collected, recorded, and reported as weekly mean exposure concentrations (Tables I2 and I3). During the 2-year studies, the time-weighted-average concentrations of toluene for each exposure group were 1.3, 119.9, 593.2, and 1,179 ppm for target concentrations of 0, 120, 600, and 1,200 ppm.

Studies for the detection of toluene aerosol in the 1,200-ppm chamber were conducted with a Sibata® P-5 Digital Dust Indicator (2-year studies) or in the 3,000-ppm chamber with a Model CI-252 (Climet Instrument Co.) aerosol particle counter (14-week studies). Aerosol was not detected in measurable quantitites.

The presence of detectable concentrations (more than 10 ppm) of residual toluene was determined by analyzing the atmosphere in all chambers at various times postexposure. Measurable concentrations occurred by 4 months after the studies began, and, after further evaluation, the animals and/or caging were indicated as the source of the residual toluene.

Vapor Concentration Uniformity in Chamber

The uniformity of the vapor concentration in each exposure chamber was measured five times over a 5-month period during the studies with the same system used to monitor the vapor concentration (used as a reference) and a second system with a different infrared monitor used for comparison with the reference. Four of the five tests that used this combined system indicated good chamber distribution; the range of variation from the reference was 3%-12%. In the fifth test, the range of variation was 26%; this large range was attributed to instrument variance and not to chamber inhomogeneity. In three subsequent tests that used only the second infrared monitor for both reference and comparison, variations from the reference position were 2%, 5%, and 14%.

THIRTEEN-WEEK GAVAGE STUDIES

Thirteen-week gavage studies were conducted to evaluate the cumulative toxic effects of repeated administration of toluene, to identify target organs, and to compare results with the inhalation study findings.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 18 days (rats) or 20 days (mice) and then assigned to dose groups. Rats were 6-7 weeks old when placed on study, and mice were 7-8 weeks old.

Groups of 10 rats and mice of each sex were administered 0, 312, 625, 1,250, 2,500, or 5,000 mg/kg toluene in corn oil by gavage, 5 days per week for 13 weeks.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded at the beginning of the studies and once per week thereafter. Further experimental details are summarized in Table 2.

At the end of the studies, animals were fasted overnight in stainless steel metabolism cages and urine was collected. Blood samples were taken from the orbital sinus. Analyses of blood and urine were performed. Survivors were killed, and a necropsy was performed on all animals. The brain, liver, lung, right kidney, right testis, and thymus were weighed. Histologic examinations were performed on animals that died before the end of the studies, vehicle controls, and animals that received 2,500 or 5,000 mg/kg. Selected tissues of lower dose animals were examined. Tissues and groups examined are listed in Table 2.

FOURTEEN-WEEK AND FIFTEEN-WEEK INHALATION STUDIES

Fourteen- and 15-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to toluene, to identify target organs, to compare results with the gavage study findings, and to determine the concentrations to be used in the 2-year studies.

Four- to 5-week-old male and female F344/N rats and 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 16 days, distributed to weight classes, and assigned to groups according to tables of random numbers. Feed was available ad libitum during nonexposure periods; water was available at all times. Further experimental details are summarized in Table 2.

Groups of 10 rats and 10 mice of each sex were exposed to air containing target concentrations of 0 (chamber controls), 100, 625, 1,250, 2,500, or 3,000 ppm toluene, 6.5 hours per day, 5 days per week for 65 exposures. Animals were observed two times per day; moribund animals were killed. Animal weights were recorded once per week.

Sperm morphologic and vaginal cytologic evaluations were performed on all surviving animals exposed at 0, 100, 625, or 1,250 ppm toluene (methods are described in Appendix G). At the end of the studies, blood was collected from the orbital sinus plexus of unfasted animals. Hematologic and biochemical analyses were performed.

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF TOLUENE

Thirteen-Week Gavage Studies	Fourteen-Week and Fifteen-Week Inhalation Studies	Fifteen-Month and Two-Year Inhalation Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
10 males and 10 females of each species	10 males and 10 females of each species	60 males and 60 females of each species
Doses		
0, 312, 625, 1,250, 2,500, or 5,000 mg/kg toluene in corn oil by gavage; dose vol--10 ml/kg	0, 100, 625, 1,250, 2,500, or 3,000 ppm toluene by inhalation	Rats--0, 600, or 1,200 ppm toluene by inhalation; mice--0, 120, 600, or 1,200 ppm
Date of First Dose		
Rats--5/19/81; mice--5/21/81	11/12/81	Rats--9/27/82; mice--11/8/82
Date of Last Dose		
Rats--8/17/81; mice--8/20/81	Rats--2/25/82; mice--2/18/82	2 y: rats--9/14/84; mice--10/26/84
Duration of Dosing		
5 d/wk for 13 wk	6.5 h/d, 5 d/wk for 14 wk (mice) or 15 wk (rats)	6.5 h/d, 5 d/wk for 15 mo or 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and then 1 × wk	Observed 2 × d; weighed initially and then 1 × wk	Observed 2 × d; weighed 1 × wk for 13 wk, 1 × 4 wk to wk 92, and then 1 × 2 wk
Method of Animal Kill		
Carbon dioxide	Intraperitoneal injection of sodium pentobarbital, followed by exsanguination	Intraperitoneal injection of sodium pentobarbital, followed by exsanguination
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all animals; the following tissues examined for vehicle controls, 2,500 and 5,000 mg/kg groups, and all animals dying before the end of the studies: adrenal glands, aorta, brain, cecum, colon, duodenum, esophagus, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), prostate/testes or ovaries/uterus, rectum, regional lymph nodes (mice), salivary glands, spinal cord, spleen, sternebrae including marrow, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Tissues examined in other groups include brain, kidneys, liver, and urinary bladder. Blood and urine collected for analysis before terminal kill; organs weighed at necropsy	Necropsy performed on all animals; histologic exams performed on all controls, 2,500- and 3,000-ppm groups, and all animals dying before the end of the studies. Tissues examined include: adrenal glands, aorta, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, femur, gallbladder (mice), heart, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, mesenteric lymph nodes, nasal tissue, pancreas, parathyroid glands, pituitary gland, preputial gland, rectum, salivary glands, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Sternum examined for the 3,000-ppm group and animals dying before the end of the studies. Blood collected for analysis before terminal kill; organs weighed at necropsy. Sperm morphologic and vaginal cytologic exams performed for all surviving animals in the control, 100-, 625-, and 1,250-ppm groups	Necropsy and histologic exams performed on all animals except 3 high dose female mice; the following tissues examined: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, femur including marrow, gross lesions and tissue masses with regional lymph nodes, heart and aorta, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), rectum, salivary glands, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Blood taken for hematologic analysis before scheduled kill and organs weighed at necropsy for 10 male rats, 10 female rats, and 10 female mice from each group at 15 mo
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF TOLUENE (Continued)

Thirteen-Week Gavage Studies	Fourteen-Week and Fifteen-Week Inhalation Studies	Fifteen-Month and Two-Year Inhalation Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory		
International Research and Development Corporation	International Research and Development Corporation	International Research and Development Corporation
Method of Animal Identification		
Rats--ear tag; mice--toe clip	Rats--ear tag; mice--toe clip	Rats--ear tag; mice--toe clip
Time Held Before Study		
Rats--18 d; mice--20 d	16 d	Rats--12 d; mice--26 d
Age When Placed on Study		
Rats--6-7 wk; mice--7-8 wk	Rats--6-7 wk; mice--8 wk	Rats--6-7 wk; mice--9-10 wk
Age When Killed		
Rats--19-20 wk; mice--20-21 wk	21-22 wk	15 mo: rats--72-73 wk; mice--75-76 wk; 2 y: rats--110-111 wk; mice--113-114 wk
Necropsy Dates		
Rats--8/18/81; mice--8/20/81	Rats--2/23/82-2/26/82; mice--2/16/82-2/19/82	15 mo: rats--12/28/84-12/29/84; female mice--2/7/84; 2 y: rats--9/24/84-9/28/84; mice--11/5/84-11/9/84
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 13-wk studies	Same as 13-wk studies
Diet		
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies, but feed removed during exposure	Same as 14- and 15-wk studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 13-wk studies	Same as 13-wk studies
Bedding		
Beta Chips hardwood bedding (Northeastern Products, Inc., Warrensburg, NY)	None	None
Cages		
Polycarbonate	Stainless steel wire mesh (Unifab, Inc., Portage, MI)	Same as 14- and 15-wk studies
Cage Filters		
Nonwoven polyester fiber	None	None
Animals per Cage		
5	1	1
Other Chemicals on Study in the Same Room		
None	None	None

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF TOLUENE (Continued)

Thirteen-Week Gavage Studies	Fourteen-Week and Fifteen-Week Inhalation Studies	Fifteen-Month and Two-Year Inhalation Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Room or Chamber (for Inhalation Studies) Environment		
Temp--mean, 72.4° F, range, 63°-82° F; hum--mean, 59.8%, range, 44%-82%; fluorescent light 12 h/d	Temp--74°-80° F during exposure; hum--45%-55% during exposure; fluorescent light 12 h/d	Temp--69°-81° F; hum--23%-75%; fluorescent light 12 h/d; 12-14 room air changes/h

At the end of the 14- and 15-week studies, survivors were anesthetized with sodium pentobarbital and killed by abdominal aorta incision. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. The brain, heart, liver, lungs, right kidney, right testis, and thymus of all animals surviving to the end of the studies were weighed. Histologic examinations were performed on animals that died before the end of the studies, controls, and animals that were exposed at 2,500 and 3,000 ppm. A bone marrow examination was performed on selected animals. Tissues and groups examined are listed in Table 2.

FIFTEEN-MONTH AND TWO-YEAR STUDIES

Study Design

Groups of 60 rats of each sex were exposed to toluene at target concentrations of 0 (chamber controls), 600, or 1,200 ppm, 6.5 hours per day, 5 days a week for 15 months or 103 weeks. Groups of 60 mice of each sex were exposed at 0, 120, 600, or 1,200 ppm on the same schedule.

At 15 months, 10 male and 10 female rats and 10 female mice from each group had blood samples taken from the orbital sinus plexus; the erythrocyte count, total leukocyte count, hemoglobin concentration, hematocrit value, leukocyte differential count, and methemoglobin concentration were determined. The brain, liver, and right kidney were weighed at necropsy, and histologic examinations were performed on controls and animals at 1,200 ppm.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The rats were quarantined at the study laboratory for 2 weeks and the mice for 4 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. Rats were placed on study at 6-7 weeks of age and mice at 9-10 weeks of age. The health of the animals was monitored during the course of the studies by serologic analysis of controls at 15 months and 2 years (Appendix E).

Animal Maintenance

Rats and mice were housed individually. Feed was removed during exposure periods; otherwise, feed (Appendix F) and water were available ad libitum. Cages were rotated during these studies. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded every 4 weeks. Body weights were recorded once per week for the first 13 weeks of the study, once every 4 weeks until week 92, and then once every 2 weeks. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead (in this study, three high dose female mice were missing after week 70). In some cases, not all samples of a particular organ were saved or some were autolyzed (e.g., mandibular lymph nodes and thymus gland in male rats, clitoral gland in 1,200-ppm female rats, and gallbladder in male and female mice). Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic evaluation. Tissues examined are listed in Table 2.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis in the potential target organs, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends such as the nose and kidney in rats.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were examined by the PWG. The PWG, which included the quality assessment pathologist and other pathologists experienced in rodent toxicology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

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

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

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

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

Analysis of Continuous Variables: For all end points, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

III. RESULTS

RATS

THIRTEEN-WEEK GAVAGE STUDIES

FIFTEEN-WEEK INHALATION STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

THIRTEEN-WEEK GAVAGE STUDIES

FOURTEEN-WEEK INHALATION STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

THIRTEEN-WEEK GAVAGE STUDIES

All rats that received 5,000 mg/kg died during the first week, and 8/10 male and 1/10 female rats that received 2,500 mg/kg died before the end of the studies (Table 3). No other compound-related deaths occurred. The final mean body weight of males that received 2,500 mg/kg was 19% lower than that of vehicle controls. Clinical signs included prostration, hypoactivity, ataxia, piloerection, lacrimation, and excessive salivation in the 2,500 and 5,000 mg/kg groups and body tremors in the 2,500 mg/kg groups. These signs reflect onset of death. The relative liver and kidney weights for female rats that received 1,250 or 2,500 mg/kg and for males that received 625 or 1,250 mg/kg were increased relative to those for vehicle controls (Table 4). The relative heart weights for female rats that received 1,250 or 2,500 mg/kg were increased compared with that for vehicle controls. None of the differences in the results of the hematologic or serum chemical analyses (Appendix H) or urinalyses was considered to be biologically meaningful. Several increases and decreases were observed (Table H1). Necrosis of the brain, consisting of neuronal necrosis in the dentate gyrus and Ammons horn of the hippocampus, was seen in male and female rats that received 1,250 or 2,500 mg/kg (Table 5). In addition to the hippocampal lesions, necrosis and/or mineralization was present in the granular cell layer of the cerebellar cortex. Hemorrhage was present in the mucosa, submucosa, or muscularis of the urinary bladder of male and female rats in the two highest dose groups. Kidney sections were examined in particular for the occurrence of hyaline droplets, and there was no evidence of an increase in the proximal tubules of the kidney of exposed rats.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	127 ± 3	331 ± 6	+204 ± 5	
312	10/10	128 ± 3	344 ± 6	+216 ± 5	104
625	10/10	126 ± 3	350 ± 6	+224 ± 5	106
1,250	10/10	127 ± 3	340 ± 6	+213 ± 4	103
2,500	(d) 2/10	127 ± 3	269 ± 16	+148 ± 20	81
5,000	(e) 0/10	127 ± 3	(f)	(f)	(f)
FEMALE					
0	10/10	107 ± 2	201 ± 3	+94 ± 2	
312	10/10	107 ± 2	200 ± 4	+93 ± 2	100
625	10/10	106 ± 2	195 ± 4	+89 ± 3	97
1,250	10/10	107 ± 2	202 ± 3	+95 ± 2	100
2,500	(e) 9/10	108 ± 2	200 ± 4	+91 ± 3	100
5,000	(e) 0/10	107 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 3,3,6,7,7,8,8,10
(e) Week of death: all 1
(f) No data are reported due to 100% mortality in this group.

TABLE 4. ANALYSIS OF SELECTED ORGAN WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE (a)

Organ	Vehicle Control	312 mg/kg	625 mg/kg	1,250 mg/kg	2,500 mg/kg
MALE					
Number weighed	10	10	10	10	(b) 2
Body weight (grams)	315 ± 6.2	328 ± 5.8	329 ± 5.8	321 ± 6.4	238 ± 7.5
Brain					
Absolute	1,828 ± 12	1,810 ± 28	1,835 ± 17	1,795 ± 18	*1,544 ± 48
Relative	5.8 ± 0.09	5.5 ± 0.07	5.6 ± 0.08	5.6 ± 0.10	6.5 ± 0.003
Heart					
Absolute	1,058 ± 28	1,110 ± 33	1,120 ± 38	1,115 ± 26	1,114 ± 10
Relative	3.4 ± 0.07	3.4 ± 0.12	3.4 ± 0.08	3.5 ± 0.09	*4.7 ± 0.11
Right kidney					
Absolute	1,084 ± 14	1,159 ± 34	*1,213 ± 39	**1,292 ± 34	*1,227 ± 114
Relative	3.5 ± 0.06	3.5 ± 0.07	*3.7 ± 0.06	**4.0 ± 0.06	**5.1 ± 0.32
Liver					
Absolute	10,490 ± 360	11,310 ± 300	*11,850 ± 390	**14,400 ± 480	*14,130 ± 1,220
Relative	33.3 ± 0.81	34.5 ± 0.68	*35.9 ± 0.68	**45.0 ± 1.69	**59.4 ± 3.28
FEMALE					
Number weighed	10	10	10	10	9
Body weight (grams)	183 ± 3.2	182 ± 3.5	175 ± 3.8	181 ± 2.7	180 ± 3.4
Brain					
Absolute	1,718 ± 19	1,688 ± 30	1,698 ± 24	1,693 ± 19	**1,625 ± 17
Relative	9.4 ± 0.22	9.3 ± 0.13	9.7 ± 0.15	9.4 ± 0.12	9.1 ± 0.18
Heart					
Absolute	693 ± 16	703 ± 27	692 ± 25	*753 ± 12	**790 ± 26
Relative	3.8 ± 0.08	3.9 ± 0.10	4.0 ± 0.11	**4.2 ± 0.05	**4.4 ± 0.13
Right kidney					
Absolute	686 ± 12	676 ± 19	652 ± 36	*733 ± 18	**803 ± 26
Relative	3.8 ± 0.08	3.7 ± 0.07	3.7 ± 0.17	**4.1 ± 0.08	**4.5 ± 0.12
Liver					
Absolute	5,596 ± 112	5,822 ± 177	5,730 ± 225	**6,780 ± 162	**8,918 ± 335
Relative	30.7 ± 0.67	31.9 ± 0.46	32.7 ± 0.87	**37.5 ± 0.68	**49.6 ± 1.53

(a) Mean in milligrams per gram necropsy body weight (relative) or milligrams (absolute) unless otherwise specified ± standard error; P values are vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Sample size was inadequate for reliable statistical comparisons with vehicle controls.
*P<0.05
**P<0.01

TABLE 5. NUMBERS OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE (a)

Site/Lesion	Vehicle Control	312 mg/kg	625 mg/kg	1,250 mg/kg	2,500 mg/kg	5,000 mg/kg
MALE						
Brain						
Necrosis	0	0	0	**6	**8	0
Urinary bladder						
Hemorrhage	0	(b) 0	0	0	2	**6
FEMALE						
Brain						
Necrosis	0	0	0	0	**7	0
Urinary bladder						
Hemorrhage	0	0	0	0	0	3

(a) Ten animals were examined in each group unless otherwise specified. All rats at 5,000 mg/kg and one female at 2,500 mg/kg died during week 1.
(b) Nine animals were examined.
**$P < 0.01$ vs. the vehicle controls

FIFTEEN-WEEK INHALATION STUDIES

Eight of 10 male rats exposed at 3,000 ppm died during week 2 (Table 6). The final mean body weights of rats exposed at 2,500 or 3,000 ppm were 15% or 25% lower than that of controls for males or 15% or 14% lower for females. Clinical signs included dyspnea in all exposed groups, except males exposed at 3,000 ppm and females exposed at 1,250 ppm, and ataxia in rats exposed at 2,500 or 3,000 ppm; other clinical signs observed in the gavage studies were not observed in these inhalation studies. The relative weights of the heart, liver, and kidney for female rats exposed at 2,500 or 3,000 ppm, of the kidney and liver for male rats exposed at 1,250 or 2,500 ppm, and of the heart for male rats exposed at 2,500 ppm were increased compared with those for controls (Table 7). None of the differences in the results of the hematologic or serum chemical analyses was considered to be biologically meaningful (Table H2). Plasma cholinesterase activity decreased as the exposure concentration increased, and the leukocyte count was decreased for female rats at 1,250 ppm or higher. No compound-related effects were seen on sperm or on the estrous cycle. The toxic lesions seen in animals exposed by gavage (see Table 5) were not observed in animals exposed by inhalation.

Dose Selection Rationale: Because of the decreases in body weights in each sex at 2,500 and 3,000 ppm, deaths in the 3,000-ppm males, and, to a lesser extent, the increases in relative organ weights, inhalation exposure concentrations selected for rats for the 15-month and 2-year studies were 0, 600, or 1,200 ppm toluene, 6.5 hours per day, 5 days per week. Also considered useful in the selection of exposure concentrations was the lack of any toxicity or carcinogenicity findings from a previously reported inhalation study using the same strain of rats exposed at 0, 30, 100, or 300 ppm (Gibson and Hardisty, 1983).

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIFTEEN-WEEK INHALATION STUDIES OF TOLUENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	177 ± 4	356 ± 4	+179 ± 4	
100	10/10	186 ± 6	366 ± 6	+180 ± 4	103
625	10/10	187 ± 5	361 ± 6	+174 ± 6	101
1,250	10/10	181 ± 5	360 ± 7	+179 ± 6	101
2,500	10/10	177 ± 5	302 ± 4	+125 ± 4	85
3,000	(e) 2/10	152 ± 4	268 ± 26	+134 ± 25	75
FEMALE					
0	10/10	127 ± 2	211 ± 3	+84 ± 2	
100	10/10	132 ± 3	210 ± 2	+78 ± 3	100
625	10/10	129 ± 3	213 ± 4	+84 ± 4	101
1,250	10/10	127 ± 3	209 ± 3	+82 ± 2	99
2,500	10/10	126 ± 3	180 ± 2	+54 ± 3	85
3,000	10/10	116 ± 2	182 ± 2	+66 ± 1	86

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Final body weight data represent weights taken at 14 weeks because, due to the unusually long terminal necropsy period, some animals were killed before the final weighing at 15 weeks.
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: all 2

TABLE 7. ANALYSIS OF ORGAN WEIGHTS OF RATS IN THE FIFTEEN-WEEK INHALATION STUDIES OF TOLUENE (a)

Organ	Control	100 ppm	625 ppm	1,250 ppm	2,500 ppm	3,000 ppm
MALE						
Number weighed	10	10	10	10	10	(b) 2
Body weight (grams)	356 ± 3.3	367 ± 6.5	362 ± 7.0	362 ± 7.5	**304 ± 4.4	*280 ± 29.5
Brain						
Absolute	1,825 ± 37	1,865 ± 23	1,865 ± 21	1,830 ± 24	1,753 ± 24	1,853 ± 17.5
Relative	5.1 ± 0.10	5.1 ± 0.10	5.2 ± 0.11	5.1 ± 0.13	**5.8 ± 0.11	*6.7 ± 0.64
Heart						
Absolute	955 ± 16	1,019 ± 25	971 ± 14	990 ± 24	900 ± 21	871 ± 87
Relative	2.7 ± 0.04	2.8 ± 0.04	2.7 ± 0.03	2.7 ± 0.04	**3.0 ± 0.05	**3.1 ± 0.02
Right kidney						
Absolute	1,161 ± 18	1,238 ± 27	1,206 ± 30	1,242 ± 28	1,147 ± 28	1,108 ± 100.0
Relative	3.3 ± 0.04	3.4 ± 0.05	3.3 ± 0.07	*3.4 ± 0.05	**3.8 ± 0.07	**4.0 ± 0.06
Liver						
Absolute	12,760 ± 260	13,210 ± 370	13,610 ± 360	14,110 ± 420	12,470 ± 300	13,310 ± 1,620
Relative	35.8 ± 0.58	36.0 ± 0.61	37.6 ± 0.55	**38.9 ± 0.54	**41.0 ± 0.60	**47.6 ± 0.79
Lung						
Absolute	1,187 ± 22	1,255 ± 18	1,213 ± 21	1,271 ± 38	1,139 ± 18	1,087 ± 72
Relative	3.3 ± 0.06	3.4 ± 0.05	3.4 ± 0.05	3.5 ± 0.08	**3.8 ± 0.07	**3.9 ± 0.16
Right testis						
Absolute	1,471 ± 25	1,532 ± 20	1,524 ± 21	1,538 ± 22	1,431 ± 18	1,411 ± 35
Relative	4.1 ± 0.05	4.2 ± 0.05	4.2 ± 0.05	4.3 ± 0.08	**4.7 ± 0.04	*5.1 ± 0.41
Cauda						
Absolute	143 ± 6	152 ± 8	147 ± 4	154 ± 5	--	--
Right epididymis						
Absolute	284 ± 7	304 ± 7	289 ± 4	289 ± 8	--	--
FEMALE						
Number weighed (c)	10	10	10	10	10	10
Body weight (grams)	209 ± 3.4	213 ± 2.4	213 ± 3.3	208 ± 3.2	**185 ± 2.2	**188 ± 2.8
Brain						
Absolute	1,729 ± 23	1,750 ± 21	1,729 ± 12	1,739 ± 8	1,691 ± 22	1,703 ± 27
Relative	8.3 ± 0.12	8.3 ± 0.16	8.2 ± 0.17	8.4 ± 0.12	**9.1 ± 0.14	**9.1 ± 0.23
Heart						
Absolute	646 ± 8	663 ± 10	653 ± 15	631 ± 16	613 ± 10	643 ± 8
Relative	3.1 ± 0.04	3.1 ± 0.04	3.1 ± 0.05	3.0 ± 0.07	*3.3 ± 0.07	**3.4 ± 0.05
Right kidney						
Absolute	704 ± 13	729 ± 14	717 ± 12	740 ± 17	710 ± 11	717 ± 17
Relative	3.4 ± 0.06	3.4 ± 0.07	3.4 ± 0.07	*3.6 ± 0.05	**3.8 ± 0.05	**3.8 ± 0.05
Liver						
Absolute	7,115 ± 155	7,407 ± 216	7,188 ± 121	7,172 ± 139	7,302 ± 95	**7,698 ± 156
Relative	34.1 ± 0.55	34.8 ± 0.85	33.8 ± 0.33	34.6 ± 0.46	**39.5 ± 0.54	**41.1 ± 0.54
Lung						
Absolute	(d) 944 ± 21	973 ± 15	(d) 966 ± 19	967 ± 21	909 ± 22	922 ± 16
Relative	(d) 4.5 ± 0.07	4.6 ± 0.07	(d) 4.5 ± 0.08	4.7 ± 0.08	**4.9 ± 0.10	**4.9 ± 0.08

(a) Mean in milligrams per gram of necropsy body weight (relative) or milligrams (absolute) unless otherwise specified ± standard error; P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Sample size was inadequate for reliable statistical comparisons with controls.
(c) Unless otherwise specified
(d) Lungs of nine animals were weighed.
*P<0.05
**P<0.01

FIFTEEN-MONTH STUDIES

In the nasal cavity, mild-to-moderate degeneration of the olfactory and respiratory epithelium was more obvious in toluene-exposed rats (male: control, 5/10; 600 ppm, 10/10; 1,200 ppm, 10/10; female: 2/10; 10/10; 9/10) and goblet cell hyperplasia was somewhat increased (male: 3/10; 8/10; 5/10; female: 2/10; 5/10; 6/10), whereas other lesions were seen in a few exposed rats (necrosis: three males and four females; metaplasia: one male and three females), and the incidences and severity of chronic inflammation were greater in exposed females than in controls (5/10; 9/10; 8/10). Hyperplasia of the alveolar and bronchiolar epithelium was found in two males and three females in the 1,200-ppm group and in one control female. The severity of nephropathy was slightly increased in exposed female rats. No other nonneoplastic lesions or any neoplastic lesions were observed which were considered to be related to toluene exposure. No compound-related effects were seen for relative organ weights (Table H7). Results of hematologic analyses did not suggest any compound-related effects (Table H3).

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weights of rats exposed at 1,200 ppm were 9% greater than those of controls (Table 8 and Figure 2); in the early weeks of the studies, these differences were diminished. Mean body weights of male rats exposed at 1,200 ppm were 4%-8% lower than those of controls from week 72 to the end of the study. Mean body weights of female rats exposed at 1,200 ppm were 4%-7% lower than those of controls from week 92 to the end of the study. An evaluation of mean body weights averaged over the first and second years indicates late decreases of 4%-5% for the 1,200-ppm groups. No compound-related clinical signs were recorded.

TABLE 8. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

Week on Study	Chamber Control Av. Wt. (grams)	Chamber Control Number Weighed	600 ppm Av. Wt. (grams)	600 ppm Wt. (percent of controls)	600 ppm Number Weighed	1,200 ppm Av. Wt. (grams)	1,200 ppm Wt. (percent of controls)	1,200 ppm Number Weighed
MALE								
1	103	60	109	106	60	112	109	60
2	131	60	133	102	60	140	107	60
3	161	60	165	102	60	170	105	60
4	185	60	189	102	60	193	104	60
5	200	60	210	105	59	212	106	60
6	221	60	225	102	59	222	100	60
7	233	60	236	101	59	235	101	60
8	244	60	246	101	59	245	101	60
9	251	60	255	102	59	258	103	60
10	260	60	264	102	59	267	103	60
11	270	60	272	101	59	269	100	60
12	281	60	281	100	59	280	100	60
13	285	60	286	100	59	287	101	60
16	311	60	307	99	59	306	99	60
20	335	60	332	99	59	328	98	60
24	350	60	347	99	59	342	98	60
28	362	60	359	99	59	354	98	60
32	370	60	373	101	59	366	99	59
36	381	60	376	99	59	371	97	59
40	390	60	381	98	59	368	94	(a)58
44	397	60	390	98	58	383	97	59
48	389	60	394	101	58	375	97	(a)58
52	404	(a)53	402	100	58	387	96	(a)57
56	396	(a)58	383	97	58	383	97	(a)54
60	398	59	395	99	58	384	96	(a)56
64	399	58	400	100	58	395	99	(a)58
68	403	(b)48	410	102	(b)48	391	97	(b)49
72	409	46	407	100	47	388	95	(a)46
76	411	(a)45	406	99	47	389	95	47
80	405	46	406	100	47	387	96	43
84	412	46	412	100	44	385	93	42
88	408	44	407	100	44	384	94	38
92	408	38	416	102	40	389	95	34
94	412	36	412	100	40	384	93	33
96	405	35	406	100	40	384	95	32
98	407	31	392	96	38	376	93	29
100	401	31	393	98	(a)30	371	92	(a)26
102	393	30	405	103	30	373	95	26
104	396	30	400	101	29	381	96	22
Mean for weeks								
1-13	217.3		220.8	101.6		222.3	102.3	
16-52	368.9		366.1	99.2		358.0	97.0	
56-104	403.9		403.3	99.9		384.0	95.1	

TABLE 8. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE (Continued)

Week on Study	Chamber Control Av. Wt. (grams)	Chamber Control Number Weighed	600 ppm Av. Wt. (grams)	600 ppm Wt. (percent of controls)	600 ppm Number Weighed	1,200 ppm Av. Wt. (grams)	1,200 ppm Wt. (percent of controls)	1,200 ppm Number Weighed
FEMALE								
1	85	60	93	109	60	93	109	60
2	99	60	104	105	60	106	107	60
3	113	60	118	104	60	121	108	60
4	124	60	130	105	60	131	106	60
5	132	60	139	105	60	143	108	60
6	143	60	145	101	60	146	102	60
7	149	60	150	101	60	152	102	60
8	153	60	155	101	(a) 59	156	102	60
9	156	60	160	103	60	164	105	60
10	159	60	162	102	60	168	106	60
11	163	60	168	103	60	170	104	60
12	168	60	174	104	60	173	103	60
13	171	60	175	102	60	177	103	60
16	180	60	183	102	60	184	102	60
20	192	60	192	100	60	190	99	60
24	198	60	200	101	60	198	100	59
28	203	60	207	102	60	203	100	59
32	207	60	217	105	60	212	102	59
36	218	60	220	101	60	217	100	59
40	222	(a) 59	220	99	60	213	96	(a) 58
44	228	(a) 59	232	102	60	223	98	59
48	233	60	235	101	60	227	97	(a) 58
52	238	(a) 59	239	100	60	229	96	(a) 58
56	236	60	233	99	60	227	96	(a) 58
60	245	60	241	98	59	238	97	(a) 58
64	245	59	250	102	59	247	101	58
68	257	(b) 48	259	101	(b) 48	249	97	(b) 47
72	263	48	254	97	(a) 42	256	97	48
76	267	48	262	98	48	258	96	48
80	263	48	262	100	44	256	97	48
84	270	(a) 45	265	98	44	258	96	44
88	272	46	274	101	44	262	97	42
92	280	43	281	100	(a) 43	265	95	40
94	283	41	279	99	42	264	93	36
96	280	40	275	98	41	264	94	(a) 34
98	281	38	277	99	37	267	95	34
100	282	38	281	100	37	261	93	33
102	281	36	279	99	36	266	95	31
104	287	33	284	99	35	274	96	30
Mean for weeks								
1-13	139.6		144.1	103.2		146.2	104.7	
16-52	211.9		214.5	101.2		209.6	98.9	
56-104	268.3		266.0	99.1		257.0	95.8	

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill occurred.

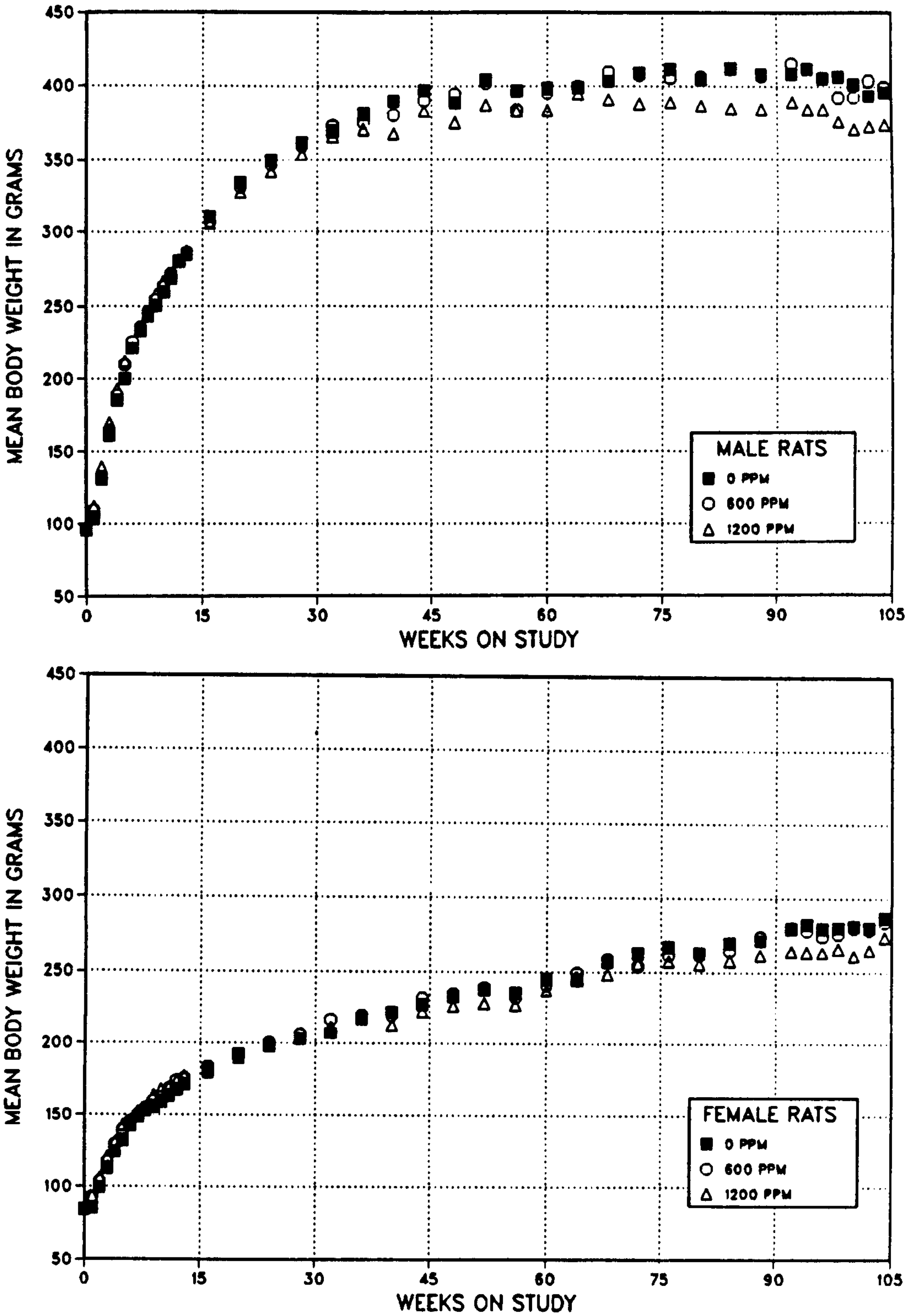


FIGURE 2. GROWTH CURVES FOR RATS EXPOSED TO TOLUENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats exposed to toluene at the concentrations used in these studies and for controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 3. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

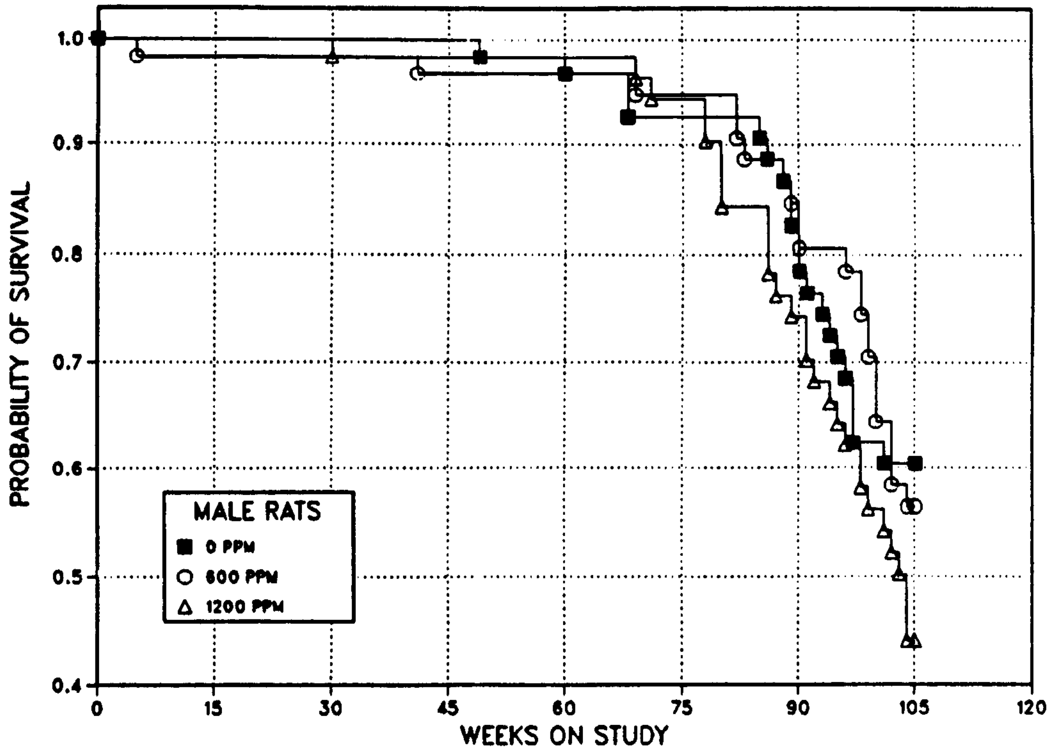
This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nose, kidney, and forestomach.

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

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
MALE (a)			
Animals initially in study	60	60	60
Animals removed at 15 mo	10	10	10
Natural deaths	6	12	5
Moribund kills	14	11	23
Killed accidentally	1	0	0
Animals surviving until study termination	(b) 29	(b) 27	22
Mean survival (days)	641	639	630
Survival P values (c)	0.17	0.99	0.21
FEMALE (a)			
Animals initially in study	60	60	60
Animals removed at 15 mo	10	10	10
Natural deaths	7	7	6
Moribund kills	11	8	14
Animals surviving until study termination	(b) 32	35	30
Mean survival (days)	658	654	643
Survival P values (c)	0.52	0.84	0.57

(a) First day of termination period: 729
(b) Animals killed at the end of the study; an additional animal died or was killed during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.



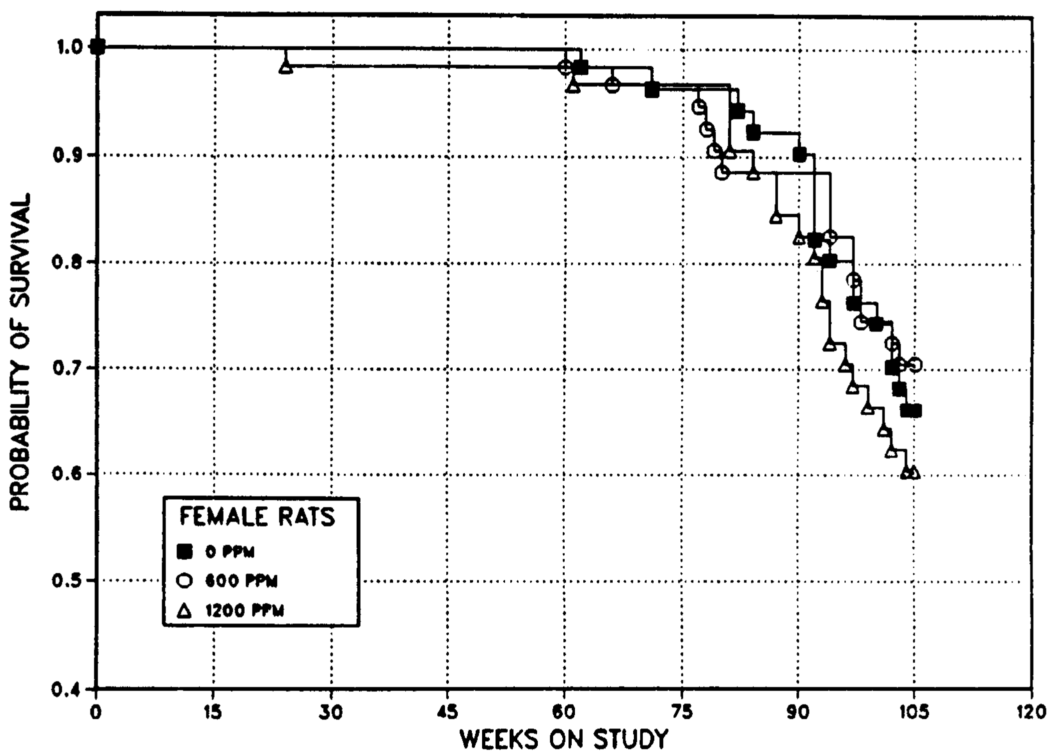


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO TOLUENE BY INHALATION FOR TWO YEARS

Nose: Erosion of the olfactory epithelium and degeneration of the respiratory epithelium were significantly ($P<0.05$) increased in exposed rats (erosion of the olfactory epithelium--male: control, 0/50; 600 ppm, 3/50; 1,200 ppm, 8/49; female: 2/49; 11/50; 10/50; degeneration of the respiratory epithelium--male: 15/50; 37/50; 31/49; female: 29/49; 45/50; 39/50). Inflammation of the nasal mucosa and respiratory metaplasia of the olfactory epithelium were observed at significantly ($P<0.05$) increased incidences in exposed female rats (inflammation of the nasal mucosa: 27/49; 42/50; 41/50; metaplasia of the olfactory epithelium: 0/49; 2/50; 6/50). This spectrum of lesions is not unusual in inhalation exposure studies of organic solvents, and the lesions were, for the most part, of mild severity. A squamous cell carcinoma of the mucosa was seen in one female rat at 1,200 ppm. Squamous cell neoplasms of the nose, nares, or nasal cavity have not been observed in 349 chamber control female F344/N rats or in 1,643 untreated controls.

Kidney: The evaluation of the kidney was done in two stages; first, a diagnostic evaluation was made on the single sections typically prepared for NTP carcinogenesis studies, and then additional sections were made and evaluated for males.

The severity of nephropathy was increased with exposure concentration in male and female rats (Table 10). Renal tubule cysts were somewhat increased in male rats at 1,200 ppm (control, 1/50; 600 ppm, 2/50; 1,200 ppm, 5/50). Renal neoplasms observed in the original evaluation include tubule adenomas in one male rat at 600 ppm and two male rats at 1,200 ppm, a carcinoma of the renal transitional epithelium in one male rat at 600 ppm, a renal tubule carcinoma in one female rat at 1,200 ppm, and a sarcoma in one female rat at 1,200 ppm. The historical incidence of renal tubule adenomas, adenocarcinomas, or carcinomas (combined) is 1/346 (0.3%) in chamber control male F344/N rats and 14/1,590 (0.9%) in untreated controls. The historical incidence of renal tubule adenomas, adenocarcinomas, or carcinomas (combined) is 1/347 (0.3%) in chamber control female F344/N rats and 2/1,639 (0.1%) in untreated controls; the historical incidence of renal sarcomas is 0/347 in chamber control female F344/N rats and 0/1,639 in untreated controls.

TABLE 10. INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

	Male			Female		
	Control	600 ppm	1,200 ppm	Control	600 ppm	1,200 ppm
Incidence	49/50	48/50	48/50	49/50	48/50	49/50
Severity (a)						
None	1	2	2	1	2	1
Minimal	1	0	1	3	4	4
Mild	19	11	10	26	17	17
Moderate	15	21	11	16	23	14
Marked	14	16	26	4	4	14
Mean severity (b)	2.8	3.0	*3.2	2.4	2.5	*2.7

(a) Number of rats with indicated severity
(b) 0 = none; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
*$P<0.05$ vs. controls

Because tubular cell neoplasms were observed in three exposed male rats and none was observed in chamber controls, the male rat kidneys were evaluated further by a more extensive sampling procedure in order to more accurately assess the actual incidences of tubular cell neoplasms of the kidney. The standard sampling method for microscopic examination involves a single longitudinal section taken from the center of the left and right kidneys, plus additional sections of any grossly visible potential neoplasms. The additional pathology procedure involved embedding the remaining pieces of each kidney which had been retained as part of the wet tissues and step sectioning the embedded tissue every millimeter to yield an average of approximately six additional sections per animal. The results of the original diagnoses, additional tissue review after eliminating duplicate diagnoses from the original review, and the combined data are presented in Table 11. Based on these data, no chemical-related increases were observed for neoplasms of the kidney.

Forestomach: Ulcers were marginally increased in exposed male rats (control, 4/50; 600 ppm, 7/50; 1,200 ppm, 9/49). A squamous cell papilloma was observed in one female rat at 1,200 ppm, and a squamous cell carcinoma was observed in a second female rat at 1,200 ppm. The historical incidence of squamous cell papillomas or carcinomas (combined) of the forestomach is 0/344 in chamber control female F344/N rats and 3/1,623 (0.2%) in untreated controls. These two neoplasms were considered to be chance occurrences and unrelated to toluene exposure.

TABLE 11. NUMBERS OF MALE RATS WITH RENAL TUBULE LESIONS IN THE FIFTEEN-MONTH AND TWO-YEAR INHALATION STUDIES OF TOLUENE

Lesion	Control	600 ppm	1,200 ppm
Number examined	60	60	60
Original single sections			
Hyperplasia	4	4	0
Adenoma	0	1	2
Carcinoma	0	0	0
Subsequent sections (a)			
Hyperplasia	0	(b) 3	2
Adenoma	5	4	0
Carcinoma	0	0	0
Composite data			
Hyperplasia	4	6	2
Adenoma	5	5	2
Carcinoma	0	0	0

(a) Six additional sections per rat
(b) Two of the rats with hyperplasia also had adenomas.

THIRTEEN-WEEK GAVAGE STUDIES

All mice that received 5,000 mg/kg died during week 1, and 4/10 male and 4/10 female mice that received 2,500 mg/kg and 1/10 female mice that received 1,250 mg/kg died before the end of the studies (Table 12). The final mean body weight of males at 2,500 mg/kg was 16% lower than that of vehicle controls. Clinical signs included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, hypoactivity, and ataxia in mice at 2,500 and 5,000 mg/kg. Relative liver weights were increased for male and female mice that received 1,250 or 2,500 mg/kg (Table 13). None of the differences in the results of the hematologic or serum chemical analyses (Table H4) or urinalyses was considered to be biologically meaningful. Myocardial fiber degeneration was observed in 3/10 males and 2/10 females at 5,000 mg/kg; all animals in these groups died during the first week of exposure.

FOURTEEN-WEEK INHALATION STUDIES

Five of 10 male mice and 10/10 female mice at 3,000 ppm died during the first 2 weeks; an additional male at 3,000 ppm, 7/10 female mice at 2,500 ppm, 1/10 female mice at 1,250 ppm, and 1/10 female mice at 625 ppm died before the end of the studies (Table 14). Final mean body weights of all exposed groups were 7%-13% lower than those of controls. Dyspnea was observed primarily at 2,500 and 3,000 ppm. The other clinical signs observed in the gavage studies were not seen in these inhalation studies. The relative liver weights for mice exposed at 625 ppm or higher and lung weights for mice exposed at 1,250 ppm or higher and the relative kidney weights for female mice exposed at 1,250 ppm or higher were greater than those for controls (Table 15). None of the differences in the results of the hematologic or serum chemical analyses was considered to be biologically meaningful (Table H5). Centrilobular hepatocellular

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	23.0 ± 0.5	32.1 ± 1.1	+9.1 ± 0.7	
312	10/10	23.3 ± 0.4	31.7 ± 0.7	+8.4 ± 0.6	98.8
625	10/10	23.3 ± 0.5	31.5 ± 0.7	+8.2 ± 0.4	98.1
1,250	10/10	23.0 ± 0.4	30.0 ± 0.8	+7.0 ± 0.6	93.5
2,500	(d) 6/10	22.6 ± 0.6	26.8 ± 0.7	+4.0 ± 0.4	83.5
5,000	(e) 0/10	22.8 ± 0.4	(f)	(f)	(f)
FEMALE					
0	10/10	19.1 ± 0.3	24.1 ± 0.4	+5.0 ± 0.3	
312	10/10	19.5 ± 0.4	25.2 ± 0.6	+5.7 ± 0.4	104.6
625	10/10	18.6 ± 0.6	23.9 ± 1.0	+5.3 ± 0.4	99.2
1,250	(g) 9/10	18.6 ± 0.5	24.0 ± 0.7	+5.4 ± 0.4	99.6
2,500	(h) 6/10	18.5 ± 0.3	23.5 ± 0.6	+5.0 ± 0.3	97.5
5,000	(e) 0/10	19.1 ± 0.5	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 2,2,9,12
(e) Week of death: all 1
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 9
(h) Week of death: 1,8,8,10

TABLE 13. ANALYSIS OF ORGAN WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE (a)

Organ	Vehicle Control	312 mg/kg	625 mg/kg	1,250 mg/kg	2,500 mg/kg
MALE					
Number weighed (b)	10	10	10	10	6
Body weight (grams)	26.4 ± 0.85	26.5 ± 0.62	26.2 ± 0.65	24.7 ± 0.52	**22.7 ± 0.71
Brain					
Absolute	427 ± 6.0	424 ± 5.6	436 ± 5.3	433 ± 4.5	433 ± 14.4
Relative	1.6 ± 0.06	1.6 ± 0.04	1.7 ± 0.04	*1.8 ± 0.03	**1.9 ± 0.07
Heart					
Absolute	144 ± 3.4	145 ± 5.1	149 ± 5.9	147 ± 4.8	130 ± 7.2
Relative	5.5 ± 0.13	5.5 ± 0.15	5.7 ± 0.15	6.0 ± 0.20	5.7 ± 0.31
Right kidney					
Absolute	222 ± 6.0	228 ± 4.9	224 ± 5.8	212 ± 7.7	**185 ± 8.6
Relative	8.4 ± 0.15	8.6 ± 0.12	8.5 ± 0.13	8.6 ± 0.22	8.1 ± 0.25
Liver					
Absolute	1,035 ± 28	1,071 ± 30	1,079 ± 35	1,073 ± 38	1,128 ± 47
Relative	39.3 ± 0.43	40.5 ± 0.84	41.2 ± 0.98	**43.4 ± 1.05	**49.7 ± 0.67
Right testis					
Absolute	(c) 117 ± 1.9	118 ± 2.4	114 ± 2.8	116 ± 3.7	108 ± 3.9
Relative	(c) 4.4 ± 0.14	4.5 ± 0.08	4.4 ± 0.06	*4.7 ± 0.11	**4.8 ± 0.06
FEMALE					
Number weighed	10	10	10	9	6
Body weight (grams)	19.4 ± 0.45	20.6 ± 0.43	19.0 ± 0.76	19.3 ± 0.47	19.0 ± 0.45
Brain					
Absolute	422 ± 6.6	445 ± 5.7	439 ± 6.0	436 ± 7.9	418 ± 12.2
Relative	2.2 ± 0.05	2.2 ± 0.05	2.4 ± 0.11	2.3 ± 0.06	2.2 ± 0.07
Heart					
Absolute	114 ± 4.7	115 ± 4.9	119 ± 5.4	118 ± 4.1	122 ± 10.1
Relative	5.9 ± 0.17	5.6 ± 0.17	6.3 ± 0.21	6.1 ± 0.19	6.4 ± 0.43
Right kidney					
Absolute	155 ± 3.7	169 ± 4.8	159 ± 4.1	160 ± 4.7	164 ± 5.1
Relative	8.0 ± 0.13	8.2 ± 0.18	8.5 ± 0.25	8.3 ± 0.11	8.7 ± 0.31
Liver					
Absolute	858 ± 38	*975 ± 27	906 ± 36	955 ± 28	**1,083 ± 31
Relative	44.1 ± 1.25	*47.3 ± 0.74	*47.8 ± 0.72	**49.4 ± 0.88	**57.0 ± 0.81

(a) Mean in milligrams per gram necropsy body weight (relative) or milligrams (absolute) unless otherwise specified ± standard error; P values are vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Testes of nine animals were weighed.
*P<0.05
**P<0.01

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF TOLUENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	20.1 ± 0.6	31.8 ± 0.8	+11.7 ± 0.5	
100	10/10	22.8 ± 0.7	29.4 ± 0.5	+6.6 ± 0.3	92.5
625	10/10	22.6 ± 0.7	29.0 ± 0.9	+6.4 ± 0.4	91.2
1,250	10/10	22.4 ± 0.6	28.9 ± 0.6	+6.5 ± 0.4	90.9
2,500	10/10	21.0 ± 1.1	27.9 ± 0.7	+6.9 ± 0.6	87.7
3,000	(d) 4/10	21.0 ± 0.3	28.8 ± 1.1	+7.8 ± 1.0	90.6
FEMALE					
0	10/10	17.5 ± 0.3	28.6 ± 0.6	+11.1 ± 0.4	
100	10/10	18.8 ± 0.2	24.9 ± 0.5	+6.1 ± 0.4	87.1
625	(e) 9/10	19.4 ± 0.6	25.1 ± 0.8	+5.7 ± 0.5	87.8
1,250	(f) 9/10	19.1 ± 0.4	25.4 ± 0.5	+6.3 ± 0.3	88.8
2,500	(g) 3/10	15.0 ± 0.7	26.7 ± 0.7	+9.0 ± 0.0	93.4
3,000	(h) 0/10	17.0 ± 0.8	(i)	(i)	(i)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1,1,2,2,2,11
(e) Week of death: 8
(f) Week of death: 13
(g) Week of death: all 1
(h) Week of death: 1,1,1,1,1,2,2,2,2,2
(i) No data are reported due to 100% mortality in this group.

TABLE 15. ANALYSIS OF ORGAN WEIGHTS OF MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF TOLUENE (a)

Organ	Control	100 ppm	625 ppm	1,250 ppm	2,500 ppm	3,000 ppm
MALE						
Number weighed (b)	10	10	10	10	10	4
Body weight (grams)	29.0 ± 0.70	28.0 ± 0.52	27.8 ± 0.93	27.3 ± 0.47	27.4 ± 0.58	27.3 ± 0.75
Brain						
Absolute	442 ± 6.3	449 ± 6.1	436 ± 4.4	456 ± 7.2	433 ± 5.6	425 ± 10.3
Relative	15.3 ± 0.40	16.1 ± 0.31	15.8 ± 0.53	16.7 ± 0.30	15.8 ± 0.29	15.7 ± 0.75
Heart						
Absolute	155 ± 2.4	150 ± 6.9	150 ± 9.4	139 ± 3.4	157 ± 7.1	153 ± 7.3
Relative	5.4 ± 0.14	5.4 ± 0.23	5.4 ± 0.22	5.1 ± 0.13	5.7 ± 0.19	5.6 ± 0.26
Right kidney						
Absolute	282 ± 10.0	282 ± 9.4	262 ± 11.5	*254 ± 7.3	*253 ± 8.4	248 ± 5.2
Relative	9.7 ± 0.24	10.1 ± 0.20	9.4 ± 0.22	9.3 ± 0.19	9.2 ± 0.19	9.1 ± 0.14
Liver						
Absolute	1,482 ± 31	1,481 ± 38	1,425 ± 48	1,519 ± 38	**2,106 ± 63	**2,026 ± 48
Relative	51.3 ± 1.29	52.9 ± 0.80	51.3 ± 0.54	*55.7 ± 1.26	**77.0 ± 2.18	**74.4 ± 0.67
Lung						
Absolute	172 ± 3.9	173 ± 4.5	174 ± 6.7	(c) 173 ± 4.0	173 ± 3.5	183 ± 6.3
Relative	6.0 ± 0.09	6.2 ± 0.17	6.3 ± 0.18	(c) 6.3 ± 0.16	*6.3 ± 0.07	*6.7 ± 0.41
Right testis						
Absolute	113 ± 5.8	121 ± 2.8	114 ± 4.2	117 ± 2.9	(c) 100 ± 5.9	104 ± 6.3
Relative	3.9 ± 0.14	*4.3 ± 0.05	4.1 ± 0.11	4.3 ± 0.07	(c) 3.7 ± 0.15	3.8 ± 0.19
FEMALE						
Number weighed (b)	10	10	9	9	3	0
Body weight (grams)	25.3 ± 0.58	23.3 ± 0.47	23.8 ± 0.60	23.7 ± 0.33	26.0 ± 0.58	--
Brain						
Absolute	462 ± 8.0	463 ± 8.3	468 ± 6.9	466 ± 7.0	453 ± 19.3	
Relative	18.4 ± 0.63	19.9 ± 0.38	19.7 ± 0.43	19.7 ± 0.28	17.4 ± 0.91	--
Heart						
Absolute	127 ± 4.4	119 ± 3.1	(d) 125 ± 3.5	125 ± 2.5	148 ± 4.7	
Relative	5.0 ± 0.18	5.1 ± 0.07	(d) 5.3 ± 0.11	5.3 ± 0.09	**5.7 ± 0.11	--
Right kidney						
Absolute	182 ± 5.9	176 ± 5.3	183 ± 7.5	183 ± 5.5	208 ± 3.2	
Relative	7.2 ± 0.28	7.6 ± 0.16	7.7 ± 0.21	*7.7 ± 0.15	*8.0 ± 0.15	--
Liver						
Absolute	1,293 ± 17	1,251 ± 30	1,300 ± 44	*1,417 ± 35	**2,058 ± 189	
Relative	51.3 ± 1.09	53.7 ± 0.89	*54.6 ± 0.92	**59.9 ± 1.54	**78.9 ± 5.57	--
Lung						
Absolute	169 ± 5.8	175 ± 4.3	(e) 175 ± 6.8	178 ± 6.5	188 ± 4.3	
Relative	6.7 ± 0.22	**7.5 ± 0.20	*(e) 7.3 ± 0.19	**7.5 ± 0.22	7.3 ± 0.26	--

(a) Mean in milligrams per gram of necropsy body weight (relative) or milligrams (absolute) unless otherwise specified ± standard error; P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Organs of nine animals were weighed.
(d) Organs of eight animals were weighed.
(e) Organs of seven animals were weighed.
*P<0.05
**P<0.01

hypertrophy was observed in 10/10 male mice at 2,500 ppm and 4/6 male mice at 3,000 ppm. No effects on sperm count or motility or on the estrous cycle were seen.

Dose Selection Rationale: Because of body weight decreases, deaths in the 3,000-ppm group of each sex, deaths in the 2,500-ppm females, dyspnea and liver hypertrophy at 2,500 and 3,000 ppm, and differences in body weights observed for most exposed groups, inhalation exposure concentrations selected for mice for the 15-month and 2-year studies were 0, 120, 600, or 1,200 ppm toluene, 6.5 hours per day, 5 days per week. A top dose of 1,200 ppm was used to match the top dose for rats; three exposure concentrations were chosen to permit an adequate study if the top dose proved to be too high for good health maintenance.

FIFTEEN-MONTH STUDIES

Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1,200 ppm, and one female mouse exposed at 1,200 ppm had an adenocarcinoma of the lung. No other lesions were observed which were considered to be related to toluene exposure. No compound-related effects were seen on relative organ weights (Table H8) or on results of hematologic analyses (Table H6).

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weights for all exposed groups of mice were 5%-14% higher than those of controls; these differences diminished rather quickly (Table 16 and Figure 4). Mean body weights of male mice at 1,200 ppm were generally similar to or somewhat higher than those of controls throughout the study. Mean body weights of female mice at 1,200 ppm were 4%-9% lower than those of controls from week 36 to week 76 and from week 88 to week 96. The yearly averages of the mean body weights of males were similar among groups, and those of females in the low and top exposure groups were about 4% lower than those of controls in the second year. No compound-related clinical signs were observed.

TABLE 16. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

Week on Study	Chamber Control		120 ppm			600 ppm			1,200 ppm		
	Av. Wt. (grams)	Number Weighed	Av. Wt. (grams)	Wt. (percent of controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of controls)	Number Weighed
MALE											
1	24.1	60	25.4	105.4	60	26.1	108.3	60	26.0	107.9	60
2	26.5	(a) 59	26.9	101.5	60	27.4	103.4	60	27.3	103.0	60
3	27.5	60	27.9	101.5	60	28.0	101.8	60	29.0	105.5	60
4	28.9	60	28.9	100.0	60	29.6	102.4	60	29.5	102.1	60
5	29.6	60	29.2	98.6	60	28.9	97.6	60	29.0	98.0	60
6	29.6	60	29.8	100.7	60	29.9	101.0	60	29.8	100.7	59
7	30.4	60	30.1	99.0	60	30.5	100.3	60	31.0	102.0	59
8	30.8	60	30.5	99.0	60	30.8	100.0	60	31.5	102.3	(a) 58
9	31.5	60	30.8	97.8	60	30.9	98.1	60	31.4	99.7	59
10	31.5	60	31.3	99.4	60	31.1	98.7	60	31.5	100.0	59
11	31.8	60	31.4	98.7	60	31.8	100.0	60	32.1	100.9	59
12	31.9	60	31.7	99.4	60	31.8	99.7	60	32.8	102.8	59
13	32.3	60	32.1	99.4	60	32.6	100.9	60	33.2	102.8	59
16	33.0	60	32.3	97.9	60	33.0	100.0	60	33.6	101.8	59
20	33.3	60	32.5	97.6	60	33.1	99.4	60	33.9	101.8	59
24	33.7	60	34.0	100.9	59	34.6	102.7	60	34.4	102.1	58
28	35.1	60	34.4	98.0	59	34.7	98.9	60	35.2	100.3	58
32	34.8	60	36.0	103.4	59	36.8	105.7	60	36.0	103.4	58
36	37.4	60	36.7	98.1	59	37.8	101.1	59	37.4	100.0	(a) 57
40	37.6	60	38.4	102.1	59	39.4	104.8	58	38.0	101.1	58
44	38.4	(a) 56	38.1	99.2	59	40.3	104.9	57	39.0	101.6	56
48	39.2	56	38.1	97.2	(a) 58	39.7	101.3	(a) 52	38.3	97.7	56
52	38.1	56	38.0	99.7	59	39.3	103.1	53	34.8	91.3	53
56	36.7	55	37.0	100.8	58	38.1	103.8	(a) 48	36.3	98.9	(a) 50
60	38.1	(a) 53	38.2	100.3	(a) 54	39.2	102.9	48	38.6	101.3	52
64	37.9	47	39.2	103.4	53	39.8	105.0	44	38.1	100.5	48
68	38.7	45	39.5	102.1	52	40.7	105.2	39	37.8	97.7	45
72	38.3	44	38.4	100.3	51	39.8	103.9	37	38.9	101.6	45
76	38.1	42	37.4	98.2	46	39.1	102.6	35	38.9	102.1	40
80	37.4	37	38.0	101.6	43	38.7	103.5	(a) 30	38.7	103.5	(a) 34
84	38.5	33	38.8	100.8	38	39.9	103.6	26	38.6	100.3	(a) 32
88	37.9	30	39.0	102.9	33	40.4	106.6	26	39.8	105.0	32
92	38.8	(a) 22	37.7	97.2	26	39.3	101.3	21	39.6	102.1	28
94	37.8	22	38.3	101.3	(a) 22	39.0	103.2	21	38.7	102.4	(a) 27
96	37.4	22	36.7	98.1	25	38.2	102.1	21	39.1	104.5	27
98	37.1	21	37.4	100.8	25	37.5	101.1	20	38.1	102.7	26
100	37.1	21	37.6	101.3	24	37.1	100.0	19	37.0	99.7	24
102	36.7	20	37.1	101.1	24	36.0	98.1	19	36.7	100.0	22
104	38.0	17	37.6	98.9	22	36.9	97.1	16	38.7	101.8	19
Mean for weeks											
1-13	29.7		29.7	100.0		30.0	101.0		30.3	102.0	
16-52	36.1		35.9	99.4		36.9	102.2		36.1	100.0	
56-104	37.8		38.0	100.5		38.7	102.4		38.4	101.6	

TABLE 16. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE (Continued)

Week on Study	Chamber Control Av. Wt. (grams)	Chamber Control Number Weighed	120 ppm Av. Wt. (grams)	120 ppm Wt. (percent of controls)	120 ppm Number Weighed	600 ppm Av. Wt. (grams)	600 ppm Wt. (percent of controls)	600 ppm Number Weighed	1,200 ppm Av. Wt. (grams)	1,200 ppm Wt. (percent of controls)	1,200 ppm Number Weighed
FEMALE											
1	19.1	59	20.5	107.3	60	21.8	114.1	60	21.6	113.1	59
2	21.1	59	21.6	102.4	59	22.1	104.7	60	21.8	103.3	59
3	21.8	59	21.4	98.2	59	22.7	104.1	60	22.7	104.1	59
4	22.7	59	23.0	101.3	59	23.5	103.5	60	23.7	104.4	59
5	23.9	59	23.6	98.7	59	23.4	97.9	60	23.8	99.6	59
6	24.2	59	24.2	100.0	59	24.6	101.7	60	24.2	100.0	59
7	24.8	59	24.2	97.6	59	25.1	101.2	60	25.6	103.2	59
8	24.9	59	24.7	99.2	59	25.9	104.0	60	26.1	104.8	59
9	25.7	59	24.7	96.1	59	25.3	98.4	60	26.1	101.6	59
10	25.7	59	25.1	97.7	59	25.6	99.6	60	25.9	100.8	59
11	26.0	59	25.6	98.5	59	26.0	100.0	60	26.6	102.3	59
12	26.4	59	25.9	98.1	59	26.7	101.1	60	27.6	104.5	58
13	26.8	59	26.2	97.8	59	27.1	101.1	60	27.5	102.6	58
16	27.6	59	26.7	96.7	59	28.3	102.5	60	27.9	101.1	58
20	28.1	59	27.0	96.1	59	27.4	97.5	60	29.0	103.2	58
24	29.0	59	28.1	96.9	59	28.3	97.6	59	28.9	99.7	58
28	29.5	59	28.6	96.9	59	28.7	97.3	59	29.6	100.3	58
32	30.4	59	29.1	95.7	59	30.6	100.7	(a) 57	30.5	100.3	58
36	33.4	59	31.0	92.8	59	32.3	96.7	(a) 58	31.6	94.6	56
40	35.7	59	32.8	91.9	59	34.8	97.5	59	32.4	90.8	56
44	36.1	58	34.3	95.0	59	36.6	101.4	59	33.8	93.6	57
48	36.1	58	33.9	93.9	59	36.5	101.1	(a) 58	33.0	91.4	57
52	34.5	58	33.8	98.0	59	34.2	99.1	(a) 58	32.7	94.8	57
56	34.1	58	33.4	97.5	(a) 55	34.9	102.3	(a) 57	32.5	95.3	(a) 55
60	36.0	56	34.8	96.7	56	36.8	102.2	59	34.2	95.0	56
64	37.3	56	35.9	96.2	55	37.1	99.5	(a) 51	34.4	92.2	56
68	36.4	(b) 45	36.0	98.9	(b) 43	38.1	104.7	(b) 49	34.7	95.3	(b) 44
72	36.6	44	34.7	94.8	(a) 41	37.5	102.5	49	35.1	95.9	43
76	37.0	45	34.6	93.5	42	37.4	101.1	46	35.6	96.2	40
80	36.4	45	34.5	94.8	41	36.6	100.5	46	35.3	97.0	41
84	37.5	44	36.5	97.3	41	38.6	102.9	43	35.8	95.5	41
88	38.0	44	36.8	96.8	40	39.5	103.9	40	36.0	94.7	38
92	39.0	40	36.5	93.6	40	39.4	101.0	37	36.8	94.4	37
94	38.5	39	37.0	96.1	38	40.4	104.9	35	36.0	93.5	37
96	37.4	39	34.6	92.5	38	39.2	104.8	32	35.6	95.2	36
98	36.7	38	34.9	95.1	38	38.0	103.5	32	35.6	97.0	36
100	36.1	36	34.7	96.1	34	38.2	105.8	32	35.7	98.9	35
102	35.8	35	35.3	98.6	34	36.8	102.8	27	34.5	96.4	34
104	36.3	30	35.3	97.2	33	36.9	101.7	24	36.5	100.6	32
Mean for weeks											
1-13	24.1		23.9	99.2		24.6	102.1		24.9	103.3	
16-52	32.0		30.5	95.3		31.8	99.4		30.9	96.6	
56-104	36.8		35.3	95.9		37.8	102.7		35.3	95.9	

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill occurred.

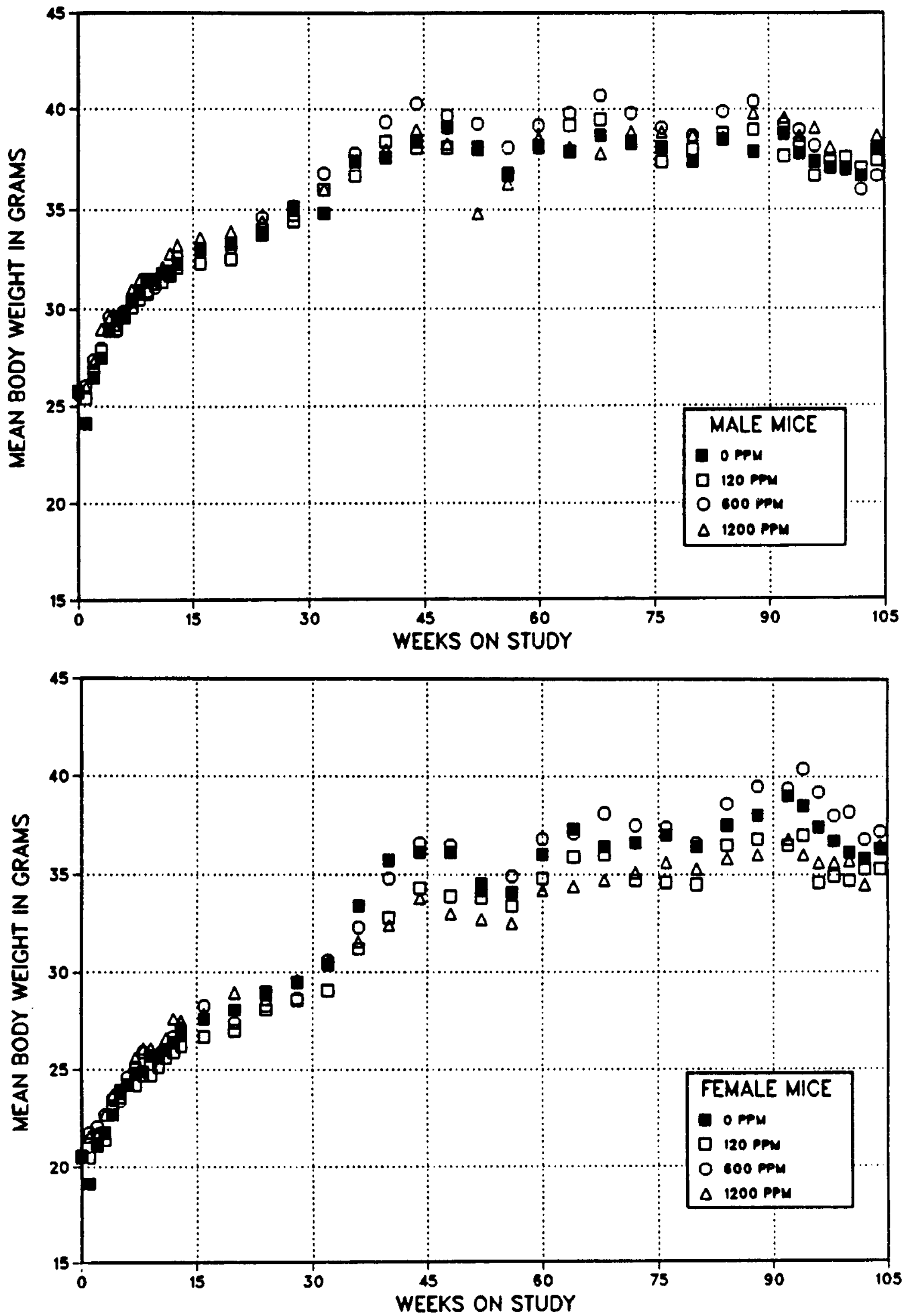


FIGURE 4. GROWTH CURVES FOR MICE EXPOSED TO TOLUENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice exposed to toluene at the doses used in these studies and for controls are shown in the Kaplan and Meier curves in Table 17 and in Figure 5. No significant differences in survival were observed between any groups of either sex. Survival in all groups of male mice, however, was inexplicably low. The particular cause or causes of early deaths in male mice were not specifically identified or recorded. However, the spectrum of nonneoplastic inflammatory lesions of the urinary and genital systems in all groups indicates that these lesions may have contributed to the early deaths (Table C5). Further, the numbers of male mice with ulcers of the prepuce (13%-23%) and/or scrotum (14%-27%) are greater than expected or than typically seen. Thus, it is reasonable to conclude that these lesions contributed to the cause of death of male mice, especially for the animals in a moribund condition. As a comparison, survival of chamber control male mice in other studies at this same laboratory is good: mean of 80% (319/400) with a range of 56%-92% at the end of the 2-year studies.

Pathology and Statistical Analyses of Results

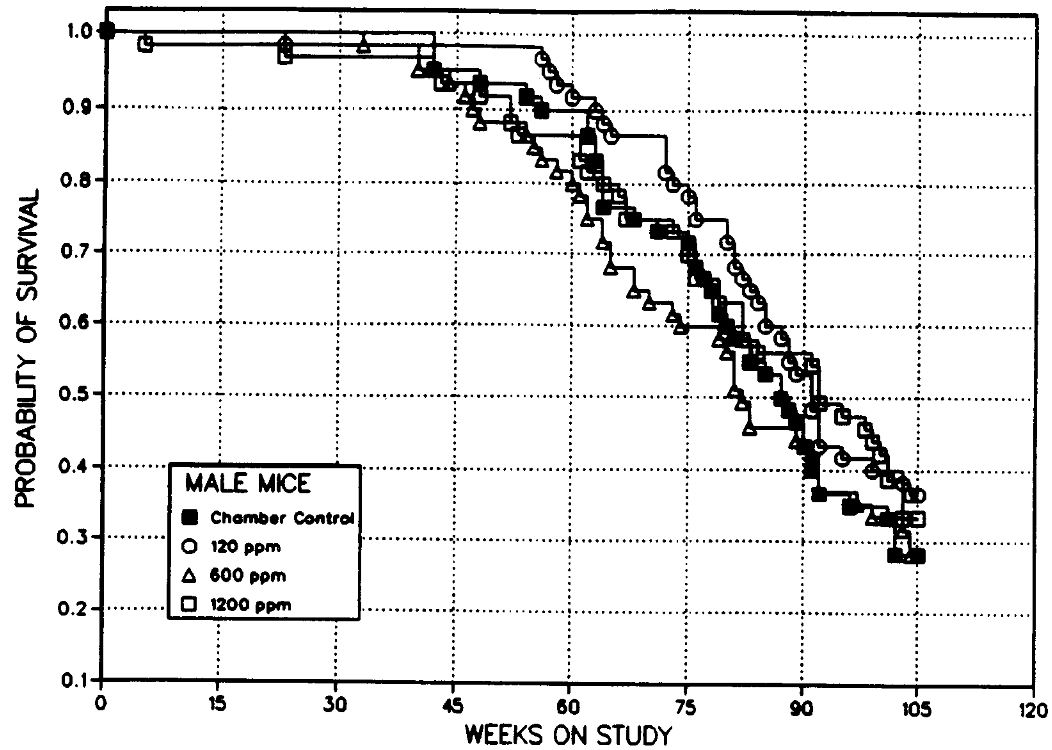
This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the pituitary gland, spleen, lung, and hematopoietic system.

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

TABLE 17. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
MALE (a)				
Animals initially in study	60	60	60	60
Natural deaths	23	20	17	22
Moribund kills	19	19	25	17
Killed accidentally	1	0	2	2
Animals surviving until study termination	17	(b) 21	16	19
Mean survival (days)	587	615	558	586
Survival P values (c)	0.99	0.36	0.74	0.66
FEMALE (a)				
Animals initially in study	60	60	60	60
Animals removed at 15 mo	10	10	10	10
Natural deaths	11	6	16	11
Moribund kills	8	8	11	3
Killed accidentally	1	3	0	1
Animals surviving until study termination	30	33	(b) 23	32
Animals missing	0	0	0	3
Mean survival (days)	635	625	633	617
Survival P values (c)	0.99	0.53	0.21	0.57

(a) First day of termination period: 729
(b) Animals killed at the end of the study; an additional animal died or was killed during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.



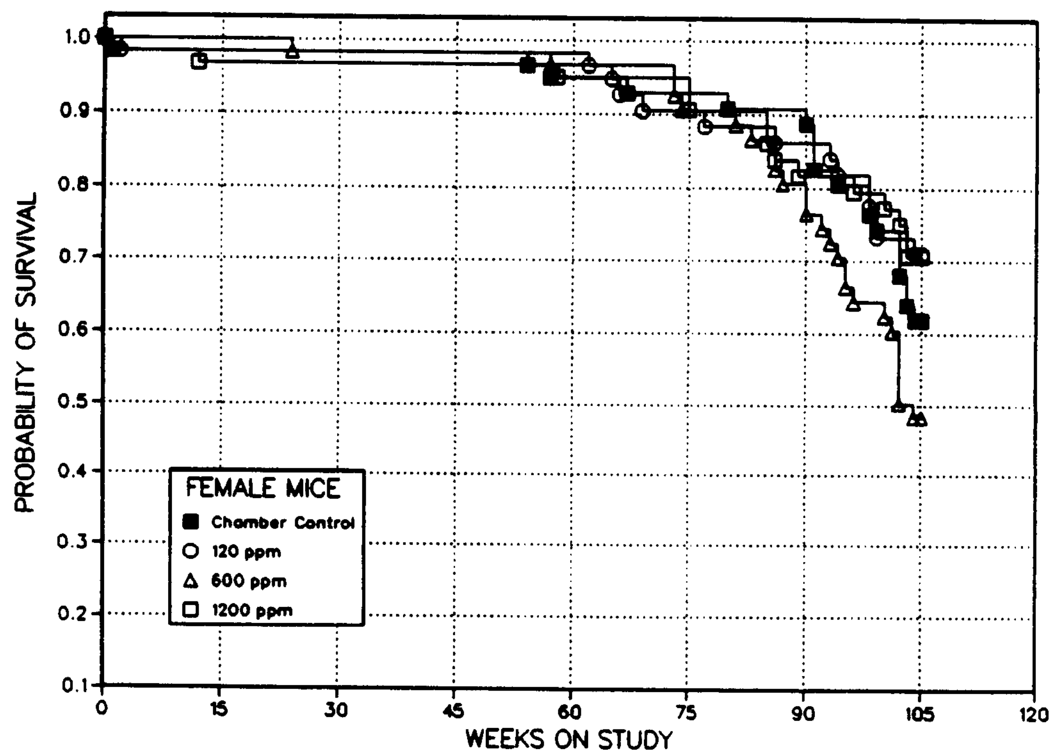


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO TOLUENE BY INHALATION FOR TWO YEARS

Pituitary Gland: The incidence of adenomas of the pars distalis in female mice at 600 ppm was statistically greater than that in controls (male: control, 0/59; 120 ppm, 2/58; 600 ppm,1/58; 1,200 ppm, 0/56; female: 12/49; 19/48; 21/49; 15/46). The increased incidence in the mid exposure group of females was considered marginal and, together with a lack of supporting hyperplasia and dose response, was not considered biologically meaningful. Adenomas of the pars intermedia were seen in 0/49 control, 1/48 120-ppm, 1/49 600-ppm, and 1/46 1,200-ppm female mice. The historical incidence of neoplasms of the pars intermedia is 1/370 (0.3%) in chamber control female B6C3F$_1$ mice and 3/1,528 (0.2%) in untreated controls. An adenoma of the pars intermedia was seen in 1/56 1,200-ppm male mice. Although the occurrence of a single adenoma in each of the three exposure groups of females might indicate a possible effect, these neoplasms were not considered to be related to toluene exposure because the incidences did not increase with dose and could have occurred by chance and because only one neoplasm was observed in males.

Spleen: Pigmentation was observed at increased incidences in exposed male mice (male: control, 4/60; 120 ppm, 9/60; 600 ppm, 11/60; 1,200 ppm, 18/59; female: 37/50; 33/50; 34/49; 28/47).

Lung: The incidences of alveolar/bronchiolar adenomas in male mice at 120 ppm and of alveolar/bronchiolar adenomas or carcinomas (combined) at 120 and 600 ppm were lower than those in controls (adenomas: control, 8/60; 120 ppm, 1/60; 600 ppm, 2/60; 1,200 ppm, 8/60; adenomas or carcinomas, combined: 9/60; 1/60; 2/60; 9/60). These decreases are not explainable by survival differences, and because the incidence in the top dose group was not decreased, this effect was not considered to be toluene related.

Hematopoietic System: The incidences of malignant lymphomas in female mice at 120 or 1,200 ppm were lower than those in controls (control, 22/50; 120 ppm, 10/50; 600 ppm, 17/50; 1,200 ppm, 11/47). The lack of a consistent exposure concentration-related decrease precludes considering the decrease at 1,200 ppm to be other than a marginal effect not related to toluene exposure.

Toluene, within a dose range of 10-1,000 µg/plate, did not induce reverse gene mutations in four strains of *S. typhimurium* (TA98, TA100, TA1535, or TA1537) when tested in a preincubation protocol in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table J1). In the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y/TK cells, toluene was positive in trials conducted with and without Aroclor 1254-induced male F344 rat liver S9 (McGregor et al., 1988; Table J2); significant responses were noted at doses of 200 µg/ml and above, which, in all but one trial, represented the highest nonlethal dose tested. Despite the statistically positive, reproducible responses observed in this assay, the overall conclusion was judged to be equivocal because the presence of a toluene/water emulsion could not be ruled out conclusively, therefore leaving a question of whether acceptable dose levels had been achieved in this assay as per the study criteria set forth in McGregor et al. (1988). In cytogenetic tests with cultured Chinese hamster ovary cells, toluene did not induce sister chromatid exchanges (Table J3) or chromosomal aberrations (Table J4) when tested with doses up to 1,600 µg/ml in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9; no induction of cell cycle delay, necessitating delayed harvest, was noted at any of the nonlethal doses tested.

IV. DISCUSSION AND CONCLUSIONS

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The alkylbenzenes are single-ring aromatic compounds containing one or more aliphatic side chains. The major products of commerce and those alkylbenzenes to which humans are most probably exposed include monomethylbenzene (toluene), ethylbenzene, isopropylbenzene, and the three dimethylbenzenes (xylenes). The industrial solvent toluene and the closely related benzene, xylenes, and ethylbenzene solvents account for more than 40 billion pounds produced each year in the United States: benzene, 11.7×10^9 lb; ethylbenzene, 9.4×10^9 lb; toluene, 7.0×10^9 lb; and xylenes, 10.9×10^9 lb (Chem. Eng. News, 1988; USITC, 1988). The aromatic six-member hydrocarbon (benzene) (NTP, 1986a; Huff et al., 1988, 1989), the monoethyl derivative (ethylbenzene), the monomethyl derivative (toluene), and the dimethyl derivatives (xylenes) (NTP, 1986b; Huff et al., 1988) were nominated and selected for toxicology and carcinogenesis characterization because each met several of the selection criteria established by the National Toxicology Program (NTP, 1986a, 1988). These four solvent congeners have considerable production volume and have widespread occupational and general population exposure. At the time these studies were designed, no adequate long-term study results were available. Additionally, long-term studies on these chemicals would provide some indications of structure-activity associations for benzene and simple alkylbenzenes.

This discussion centers on the toluene studies in F344/N rats and $B6C3F_1$ mice and compares these findings with those on benzene and xylenes (mixed) previously reported. In early 1982, using the results of the NTP short-term studies together with the preliminary findings from the Chemical Industry Institute of Toxicology long-term studies (Gibson and Hardisty, 1983) showing an apparent lack of any significant toxic effects, the NTP decided to continue with the 2-year studies described in this Technical Report. The toluene inhalation studies were conducted at exposure concentrations up to 1,200 ppm, four times higher than those used by Gibson and Hardisty (1983).

A comparison of the effects on rats and mice exposed to toluene by the gavage and inhalation routes in the current 13- or 15-week studies indicates an apparent similarity in certain clinical signs (e.g., dyspnea and ataxia) and organ weights (kidney and liver weight increases) and a difference in organs showing some nonneoplastic responses--brain and urinary bladder in the gavage studies in rats and none in particular for the rats and mice exposed by inhalation (liver hypertrophy in male mice). In any event, other than clinical signs of a usually transient toxicity and the brain lesions in the gavage studies, toluene-induced toxic effects were relatively rare by either route of short-term exposure.

For the longer term toluene studies, body weights for male and female rats were similar among the respective groups for both the 15-month and 2-year exposure periods (see Tables 8 and H7). The 1,200-ppm group of males in the 15-month study and the 1,200-ppm group of females at the end of 2 years had mean body weights 5%-9% lower than those of the controls. Body weights for male and female mice were within 5% of those of controls among groups in the 15-month and 2-year studies, except that the body weights for the 1,200-ppm group of 10 female mice examined at 15 months were approximately 8% lower than those for controls. These relatively small differences in mean body weights are within the range of normal variations observed for untreated control F344/N rats and $B6C3F_1$ mice (Haseman et al., 1985) and are considered to be only minimally associated with toluene exposure. When body weights are averaged over the second year (see Tables 8 and 16), the differences become even less meaningful.

Survival for male rats at the end of the study was slightly lower than that for untreated historical control male F344/N rats (Haseman et al., 1984, 1985), especially for the 1,200-ppm group. Survival for female rats and for male and female mice at the end of the 2-year exposure was good and similar within the particular species and gender groups, although the numbers of male mice surviving were unexpectedly low in all groups. Many of the animals dying or killed in a moribund condition had inflammatory and ulcerous lesions of the penis, prepuce, and scrotum; the lesions were considered to be factors contributing to the low survival. Courses of action that were considered but not taken involved either reducing the exposure concentrations to about 900 ppm (the midpoint between the top and mid exposure groups) or altering the frequency of all exposures to three times per week (every other day). Another option was to discontinue exposure at week 64 (survival: control, 47/60; low dose, 53/60; mid dose, 44/60; high dose, 48/60) and consider these studies as 15-month studies. None of these possibilities was adopted, and the studies were continued because the decreases in survival were observed in all groups and were not considered related to toluene exposure.

Considering these body weight and survival observations in isolation from any other effects, one might reasonably conclude that higher exposure concentrations could have been used. For mice, higher exposure concentrations might have been tolerated; yet the findings from the 14-week inhalation studies supported the selected exposure concentrations and forecast that using the top exposure concentration of 1,200 ppm was appropriate. Matsumoto et al. (1971) likewise reported organ weight to body weight increases for liver, kidney, and heart in DONRYU male rats exposed to 2,000 ppm toluene by inhalation for 18 weeks. Thus, these whole-body exposures, up to 1,200 ppm for 6 hours per day, 5 days per week for 2 years, were considered both prospectively and retrospectively to have been an adequate and sufficient exposure challenge for determining the presence or absence of a carcinogenic response.

No chemically related macroscopic or organ weight effects were observed in the groups of 10 male and 10 female rats and 10 female mice killed and examined at 15 months. Because of low survival, none of the male mice was killed for evaluation at 15 months. Microscopically, mild degeneration of the olfactory and respiratory epithelium was evident in toluene-exposed rats; in females, but not males, the severity and incidence of chronic inflammation of the nasal tissue was somewhat greater in both the 600- and 1,200-ppm groups. Necrosis and squamous metaplasia of the nasal cavity were seen in a few animals, as was hyperplasia of alveolar and bronchiolar epithelium.

For rats at the end of the 2-year exposure, no striking macroscopic alterations were observed at necropsy which were considered to be related to toluene exposure. Microscopically, nonneoplastic (toxic) effects likely due to toluene exposure were limited to mild responses in the nasal cavity and were similar to those observed in the 15-month studies. Concentration-dependent increases in the severity of nephropathy was seen in rats. Although Matsumoto et al. (1971) reported finding eosinophilic droplets in the kidney of male DONYRU rats after exposure to toluene, no evidence was found of an increase in hyaline droplets in the proximal tubules of the kidney of exposed male rats in either the 14- or 15-week gavage or inhalation studies of toluene. Other changes that usually accompany the increase in hyaline droplets ($\alpha_{2\mu}$-globulin) in the "hydrocarbon nephropathy" syndrome, such as granular casts at the junction of the inner and outer stripe of the outer medulla in short-term studies and linear mineralization of the medulla in long-term studies, also were not found in the current NTP studies. These findings suggest that $\alpha_{2\mu}$-globulin did not play a role in the exacerbation of spontaneous renal disease observed in the current NTP studies. The biologic significance of the eosinophilic droplets found by Matsumoto et al. (1971) is uncertain; the droplets could be albumin or other pigment but do not appear to be $\alpha_{2\mu}$-globulin, as best as can be determined by an examination of Kodachrome slides of kidney sections from the Matsumoto studies. It is not certain how long after the last exposure the animals were killed, which is particularly important because the $\alpha_{2\mu}$-globulin has a relatively rapid disappearance (72-96 hours) after exposure has been stopped. Further, earlier studies were conducted for 43 weeks (rats were approximately 1 year old when killed); synthesis of $\alpha_{2\mu}$-globulin is known to decrease with age (Motwani et al., 1984) and seems to parallel the amount of cellular proliferation, being greater at 3 months of age and least at 12 months (Swenberg et al., 1989).

One possible neoplastic finding from these studies was that tubular cell adenomas of the kidney on routine (single) sectioning were found in one low dose and in two high dose male rats, and another low dose male rat had a transitional epithelial carcinoma; one high dose female rat had a renal tubular cell carcinoma, and another had a sarcoma of the kidney. Because these lesions were not accompanied by the occurrence of tubular cell hyperplasia, because benzene (NTP, 1986a) and xylenes (NTP, 1986b) did not cause kidney neoplasms, although the kidney appears to be a target for other organic solvents, and, more important, because the finding of these few uncommon tumor types were possible signals for potential public health concern, the Program decided to evaluate this organ in extra detail. For each male rat, approximately six additional tissue sections were evaluated. The results of this supplementary evaluation revealed nine microscopic adenomas that were not discovered on routine sectioning--five in controls and four in the low dose group. All tubular cell neoplasms were benign. The combined diagnoses show that toluene did not cause any increases in hyperplasia, benign neoplasms, or malignant neoplasms of the kidney (see Table 11). Likewise, neither benzene nor xylenes were associated with kidney toxicity. The incidence of the five neoplasms (8.3%) found in the control male rats is the highest seen in the four NTP studies evaluated by step-sectioning of the kidney. For the three other studies, additional sections of the kidney of control male rats revealed either no increase (phenylbutazone, 0/50 to 0/50; NTP, 1989c) or an increase of two (furosemide, 1/50 to 3/50; NTP, 1989d) or three (nitrofurantoin, 0/50 to 3/50; NTP, 1989e). Thus, for the four separate control groups of male F344/N rats, the incidences of tubular cell adenomas of the kidney increased from 1/210 (0.5%) by routine sectioning to 11/210 (5.3%) by additional sectioning. This is similar to the experience of Kurokawa et al. (1983, 1986), who compared single sections vs. 15-20 sections of kidneys from F344 rats exposed to potassium bromate; in these studies, males showed an increase from one to three neoplasms in a group of 53 rats, whereas the number of neoplasms in females was zero before and after additional sections.

In contrast to the results reported by Maltoni et al. (1983, 1985) regarding increases in total malignant tumors in toluene-exposed Sprague Dawley rats (see Introduction), none of the study groups of F344/N rats or $B6C3F_1$ mice in the current studies showed a toluene-associated increase in the numbers of animals with benign or malignant tumors or total benign and/or malignant tumors. However, using the overall number of animals with tumors is not considered to be appropriate for detecting potential carcinogenic effects of chemicals, except when observed in studies of less than 18 months (IARC, 1980, 1986; Huff et al., 1985; Haseman et al., 1986).

Both rats and mice exposed to benzene exhibited chemically related nonneoplastic and neoplastic effects of the hematopoietic system, Zymbal gland, forestomach, and adrenal gland. Further, neoplasms were induced in the oral cavity in rats and in the lung, liver, harderian gland, preputial gland, ovary, and mammary gland in mice (NTP, 1986a; Huff et al., 1988, 1989). In contrast to benzene (oral intubation at concentrations of 0 and 25-200 mg/kg), no significant changes in the incidences of neoplastic or nonneoplastic lesions in rats or mice were considered to be related to exposure to toluene (other than increased severity of nephropathy in rats) or xylenes (mixed) (NTP, 1986b) for 2 years. Exposure concentrations in the current toluene studies (0 and 120-1,200 ppm) were estimated to be considerably (up to 15 times) higher than those in the benzene studies. In addition, the gavage concentration of xylenes (mixed) (0 and 250-1,000 mg/kg) in the 2-year studies was from 2.5 (rats) to 10 (mice) times greater than those of benzene. Reviews of the xylene literature generally support the results of the NTP short-term studies (NIOSH, 1975; Miller et al., 1976; Mazella et al., 1978), but no reports on 2-year or lifetime studies were found. In two papers on benzene, Maltoni et al. (1983, 1985) reported some incomplete findings from long-term studies in which Sprague Dawley rats were given 500 mg/kg xylenes in olive oil by gavage for 2 years and survivors were continued without exposure to week 141. They reported an increase in the total number of animals with malignant neoplasms in dosed vs. vehicle control males (14/40, 35% vs. 11/50) and females (22/40, 55% vs. 10/50). By comparison, after F344/N rats in the NTP studies were exposed to xylenes (mixed) for 104 weeks (NTP, 1986b), the total number of females with malignant neoplasms was not statistically increased at 500 mg/kg (16/50) compared with vehicle controls (12/50), and the total number of males with malignant neoplasms was actually decreased at 500 mg/kg (19/50) compared with vehicle controls (32/50), although this decrease was probably due to decreased survival in the dosed group. However, basing any conclusion on the overall proportion of animals with primary neoplasms (or with malignant neoplasms) is not the best approach for deciding potential carcinogenic effects of chemicals (IARC, 1980, 1986; Haseman et al., 1986).

One mechanism often proposed for observed differences in chemically induced toxic responses comes from metabolic studies whereby a chemical may modify its own toxicity or that of other chemicals by altering metabolism through induction of metabolizing enzymes. Pathiratne et al. (1986) investigated the effects of benzene, toluene, and xylenes on liver metabolism in male Sprague Dawley rats. Benzene was more potent at inducing conjugating systems, whereas xylenes were more potent at inducing cytochrome P450-dependent enzymes. Toluene was equipotent at inducing both enzyme types. The addition of methyl groups to the aromatic ring affects not only chemical-specific metabolism but also the inductive pattern of these monocyclic aromatic hydrocarbons. Thus, cytochrome P450 and related enzymes were induced to a greater degree with an increasing number of methyl groups, whereas the conjugating enzymes were affected in the opposite direction.

The key to the differences in responses between benzene and the methyl and dimethyl derivatives convincingly resides in the metabolism and the pattern of metabolic products. Benzene (NTP, 1986a; Huff et al., 1989) undergoes a complex constellation of multiple metabolic pathways leading to varied ring and ring-opened chemicals, some of which have been shown to induce cancer in animals when administered alone (catechol, Hirose et al., 1987, 1988; hydroquinone, NTP, 1989f; phenol, data considered negative or pehaps equivocal, NCI, 1980). To the contrary, toluene (and xylenes, NTP, 1986b) undergoes a simple Phase I oxidation to benzyl alcohol (no evidence of carcinogenicity; NTP, 1989a) on through benzaldehyde (NTP, 1989b) and benzoic acid (no evidence of carcinogenicity; personal communication from N. Ito, Nagoya City University, to J. Huff, NTP, 1989) and then to Phase II conjugation via mainly glycine (hippuric acid) and, to a lesser extent, by way of glucuronic acid (benzoyl glucuronide). Nearly 25% appears to be excreted unchanged, and this overall pattern pertains about equally whether the chemical is given orally or by inhalation (Pyykko et al., 1977). Small amounts of cresols are formed; these or hippurates in urine are used as biomonitors of human exposures. A postulated but never isolated metabolite is toluene oxide (Jerina et al., 1971). Ethylbenzene behaves similarly in that the major urinary metabolite is hippuric acid; following oxidation to benzoic, phenylacetic, and mandelic acids, these are excreted as glycine conjugates.

The results of the 2-year studies on benzene, toluene, and xylenes (mixed) show that methyl and dimethyl substitution on the benzene ring eliminates the carcinogenic influence of this molecule on rodents. Given the varying metabolic disposition patterns of these three congeners, these findings are perhaps not surprising.

Toluene, like benzene and its congeners and metabolites, does not appear to be a mutagen in vitro. The responses with toluene in microbial mutagenicity assays were uniformly negative, including several assays in which protocols specific for volatile chemicals were used. Results of the few in vitro assays conducted with mammalian cells for gene mutations or for cytogenetic damage were also negative. It is uncertain whether toluene, like benzene and its congeners and metabolites, is a clastogen in vivo. Single-exposure studies with toluene of specified purity were negative; mice or rats were exposed to toluene at doses up to 1,000 mg/kg and assayed for induction of chromosomal aberrations and micronucleated erythrocytes in bone marrow, and no chemical-related increases were observed (Kirkhart, 1980). On the other hand, Dobrokhotov (1972) and Lyapkalo (1973) both reported induction of chromosomal aberrations in bone marrow erythrocytes of rats exposed to toluene at 800-1,000 mg/kg per day for 12 days. Since the purity of the toluene was not specified, it is possible that the positive response could have come from benzene contamination. In some studies, benzene has been shown to be more effective when given repeatedly than when given once. Although toluene has not been tested for clastogenicity in somatic cells except in studies using a single exposure, it did not induce dominant lethal mutations in the germ cells of CD®-1 mice exposed by inhalation at concentrations up to 400 ppm for 6 hours per day, 5 days per week, for 8 weeks (LBI, 1981). The key to the differences in the genetic toxicity between benzene and its methyl and dimethyl derivatives, like those in other toxicity responses, convincingly resides in the metabolism and the pattern of metabolic products.

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

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** for male or female F344/N rats exposed to toluene at concentrations of 600 or 1,200 ppm. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice exposed by inhalation to toluene at concentrations of 120, 600, or 1,200 ppm for 2 years.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
Intestine large, cecum	(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)		1 (2%)
Intestine large, colon	(50)	*(50)	(49)
Leukemia mononuclear	1 (2%)		2 (4%)
Intestine large, rectum	(49)	*(50)	(49)
Leukemia mononuclear	1 (2%)		
Intestine small, duodenum	(50)	(50)	(49)
Leukemia mononuclear	3 (6%)	3 (6%)	1 (2%)
Intestine small, ileum	(49)	(50)	(49)
Leukemia mononuclear	2 (4%)	3 (6%)	
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small, jejunum	(50)	(50)	(49)
Adenocarcinoma, mucinous	1 (2%)		
Leukemia mononuclear	2 (4%)	2 (4%)	
Liver	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)	
Hepatocellular adenoma	4 (8%)	2 (4%)	
Histiocytic sarcoma, metastatic		1 (2%)	
Leukemia mononuclear	16 (32%)	25 (50%)	19 (38%)
Serosa, mesothelioma malignant			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Pancreas	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	7 (14%)	3 (6%)
Mesothelioma malignant			1 (2%)
Acinus, adenoma	1 (2%)		
Salivary glands	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
Stomach, forestomach	(50)	(50)	(49)
Leukemia mononuclear	3 (6%)	7 (14%)	1 (2%)
Serosa, mesothelioma malignant			1 (2%)
Stomach, glandular	(50)	(50)	(49)
Leukemia mononuclear	3 (6%)	4 (8%)	3 (6%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Carcinoma adenosquamous, metastatic, lung	1 (2%)		
Leukemia mononuclear	9 (18%)	17 (34%)	7 (14%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(50)	(50)
Capsule, fibrosarcoma, metastatic, skin		1 (2%)	
Capsule, mesothelioma malignant			1 (2%)
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma		1 (2%)	
Leukemia mononuclear	14 (28%)	16 (32%)	10 (20%)
Adrenal gland, medulla	(49)	(50)	(50)
Leukemia mononuclear	11 (22%)	16 (32%)	10 (20%)
Pheochromocytoma malignant		1 (2%)	
Pheochromocytoma, NOS	7 (14%)	7 (14%)	6 (12%)
Bilateral, pheochromocytoma, NOS		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(50)	(50)	(50)
Adenoma	2 (4%)	2 (4%)	2 (4%)
Carcinoma	1 (2%)		1 (2%)
Pituitary gland	(49)	(50)	(50)
Pars distalis, adenoma	22 (45%)	24 (48%)	18 (36%)
Pars distalis, carcinoma			1 (2%)
Pars distalis, leukemia monocytic			1 (2%)
Pars distalis, leukemia mononuclear	3 (6%)	5 (10%)	3 (6%)
Pars intermedia, leukemia mononuclear		1 (2%)	
Pars nervosa, leukemia mononuclear		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
C-cell, adenoma	5 (10%)	7 (14%)	8 (16%)
C-cell, carcinoma		1 (2%)	
Follicle, adenoma	1 (2%)	2 (4%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Preputial gland	(50)	(50)	(50)
Adenoma		1 (2%)	
Carcinoma	1 (2%)		
Leukemia mononuclear	2 (4%)	3 (6%)	
Prostate	(50)	(50)	(50)
Leukemia mononuclear		3 (6%)	
Testes	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
Bilateral, interstitial cell, adenoma	23 (46%)	27 (54%)	30 (60%)
Interstitial cell, adenoma	13 (26%)	9 (18%)	10 (20%)
Serosa, mesothelioma malignant	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	2 (4%)
Bone marrow	(50)	(50)	(50)
Leukemia mononuclear	10 (20%)	15 (30%)	12 (24%)
Lymph node	(50)	(50)	(50)
Carcinoma adenosquamous, metastatic, lung	1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	
Leukemia mononuclear	1 (2%)		2 (4%)
Iliac, leukemia mononuclear		1 (2%)	
Mediastinal, leukemia mononuclear	4 (8%)	5 (10%)	1 (2%)
Mesenteric, leukemia mononuclear	14 (28%)	20 (40%)	17 (34%)
Mesenteric, lymphoma malignant lymphocytic	1 (2%)		
Renal, carcinoma, metastatic, kidney		1 (2%)	
Renal, leukemia mononuclear	2 (4%)		
Lymph node, mandibular	(36)	(45)	(37)
Leukemia mononuclear	2 (6%)	11 (24%)	4 (11%)
Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Leukemia mononuclear	17 (34%)	25 (50%)	19 (38%)
Lymphoma malignant			1 (2%)
Capsule, mesothelioma malignant			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(44)	(46)	(46)
Carcinoma, metastatic, kidney		1 (2%)	
Carcinoma adenosquamous, metastatic, lung	1 (2%)		
Leukemia mononuclear	6 (14%)	9 (20%)	4 (9%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(48)	(49)
Fibroadenoma	1 (2%)		
Skin	(50)	(50)	(50)
Histiocytic sarcoma, metastatic		1 (2%)	
Keratoacanthoma		1 (2%)	
Subcutaneous tissue, fibroma	2 (4%)		1 (2%)
Subcutaneous tissue, fibrosarcoma		2 (4%)	1 (2%)
Tail, papilloma squamous			1 (2%)
Thoracic, subcutaneous tissue, fibroma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Fibrosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	7 (14%)	3 (6%)
Cerebrum, astrocytoma malignant		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma		1 (2%)	
Carcinoma, metastatic, kidney		1 (2%)	
Carcinoma adenosquamous	1 (2%)		1 (2%)
Fibrosarcoma, metastatic, skin		1 (2%)	
Fibrous histiocytoma, metastatic, skin			1 (2%)
Histiocytic sarcoma, metastatic		1 (2%)	
Leukemia monocytic	1 (2%)		
Leukemia mononuclear	16 (32%)	22 (44%)	14 (28%)
Osteosarcoma, metastatic, uncertain primary site			1 (2%)
Trachea	(50)	(50)	(50)
Carcinoma adenosquamous, metastatic, lung	1 (2%)		
Leukemia mononuclear	3 (6%)	5 (10%)	
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)	2 (4%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Histiocytic sarcoma, metastatic		1 (2%)	
Leukemia mononuclear	3 (6%)	10 (20%)	4 (8%)
Capsule, fibrosarcoma, metastatic, skin		1 (2%)	
Capsule, mesothelioma malignant			1 (2%)
Renal tubule, adenoma		1 (2%)	2 (4%)
Transitional epithelium, carcinoma		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
URINARY SYSTEM (Continued)			
Urinary bladder	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)	
Leukemia mononuclear	5 (10%)	10 (20%)	3 (6%)
Sarcoma	1 (2%)		
Serosa, mesothelioma malignant			1 (2%)
Transitional epithelium, papilloma			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	17 (34%)	26 (52%)	19 (38%)
Lymphoma malignant lymphocytic	1 (2%)		
Leukemia monocytic	1 (2%)		1 (2%)
Mesothelioma malignant	1 (2%)		1 (2%)
Hemangiosarcoma		1 (2%)	
Lymphoma malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Interval sacrifice	10	10	10
Terminal sacrifice	29	27	22
Moribund	14	11	23
Dead	6	9	5
Accident	1		
Natural death		3	
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	48	49
Total primary neoplasms	108	122	107
Total animals with benign neoplasms	45	46	47
Total benign neoplasms	75	77	73
Total animals with malignant neoplasms	23	31	26
Total malignant neoplasms	26	37	28
Total animals with secondary neoplasms ***	1	3	2
Total secondary neoplasms	4	12	3
Total animals with malignant neoplasms-- uncertain primary site			1
Total animals with neoplasms-- uncertain benign or malignant	7	8	6
Total uncertain neoplasms	7	8	6

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: CHAMBER CONTROL

WEEKS ON STUDY	049	060	068	068	085	086	088	089	089	090	090	091	093	094	095	096	097	097	097	101	105	105	105	105	105
CARCASS ID	141	531	311	241	161	481	321	471	421	201	371	271	101	171	331	391	351	491	521	131	031	251	401	511	571
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymphoma malignant lymphocytic																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, mucinous																									
Leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X											
Leukemia mononuclear		X				X	X	X		X	X	X	X					X			X				X
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X																		
Acinus, adenoma																			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X						X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X																		
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous, metastatic, lung			X																						
Leukemia mononuclear		X				X	X					X	X					X							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X	X				X	X					X			X				X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X	X				X	X					X							
Pheochromocytoma, NOS								X										X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X															X		
Carcinoma																									
Parathyroid gland	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X		X	X	X			X		X	X	X	X		X			X			
Pars distalis, leukemia mononuclear																		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
C-cell, adenoma					X																				
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																							
Bilateral, interstitial cell, adenoma													X					X			X	X			X
Interstitial cell, adenoma							X	X		X					X	X				X			X	X	
Serosa, mesothelioma malignant																									

+: Tissue examined microscopically
 : Not examined
−: Present but not examined microscopically
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	601	021	041	061	211	461	591	121	151	191	431	561	581	071	081	291	301	341	381	051	091	111	181	231	441	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X												X		3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear												X												X		2
Lymphoma malignant lymphocytic								X																		1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, mucinous																						X				1
Leukemia mononuclear												X												X		2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																		X			X				X	4
Leukemia mononuclear							X					X	X						X					X		16
Mesentery													+											+		2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Acinus, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																								X		3
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma adenosquamous, metastatic, lung																										1
Leukemia mononuclear												X												X	X	9
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X					X							X					X	X	14
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear							X					X							X					X		11
Pheochromocytoma, NOS												X	X	X					X		X					7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma																									X	1
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X		X		X	X			X	X	X	X	X		X							22
Pars distalis, leukemia mononuclear												X												X		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C-cell, adenoma						X				X										X		X				5
Follicle, adenoma																									X	1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Leukemia mononuclear												X												X		2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Bilateral, interstitial cell, adenoma	X	X	X		X	X	X	X	X	X				X	X			X		X	X	X	X	X	X	23
Interstitial cell, adenoma				X							X	X					X		X							13
Serosa, mesothelioma malignant						X																				1

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

WEEKS ON STUDY	049	060	068	068	085	086	088	089	089	090	090	091	093	094	095	096	097	097	097	101	105	105	105	105	105
CARCASS ID	141	531	311	241	161	481	321	471	421	201	371	271	101	171	331	391	351	491	521	131	031	251	401	511	571
HEMATOPOIETIC SYSTEM																									
Blood	+																						+		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X				X	X	X					X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous, metastatic, lung			X																						
Leukemia mononuclear																									
Mediastinal, leukemia mononuclear						X					X		X												
Mesenteric, leukemia mononuclear		X				X		X			X	X	X					X			X				X
Mesenteric, lymphoma malignant lymphocytic																									
Renal, leukemia mononuclear		X																							
Lymph node, mandibular	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X				X	X	X		X	X	X	X					X			X				X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+
Carcinoma adenosquamous, metastatic, lung			X																						
Leukemia mononuclear		X				X						X	X												
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma										X															
Thoracic, subcutaneous tissue, fibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X						X												
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous			X																						
Leukemia monocytic																									
Leukemia mononuclear		X				X	X	X		X	X	X	X					X			X				X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous, metastatic, lung			X																						
Leukemia mononuclear		X										X													
SPECIAL SENSES SYSTEM																									
Eye																		+							
Zymbal gland																				+					
Carcinoma																				X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X											X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X											X							
Sarcoma																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	601	021	041	061	211	461	591	121	151	191	431	561	581	071	081	291	301	341	381	051	091	111	181	231	441	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood															+					+						4
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X	X											X		10
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma adenosquamous, metastatic, lung																										1
Leukemia mononuclear																								X		1
Mediastinal, leukemia mononuclear																								X		4
Mesenteric, leukemia mononuclear							X					X	X											X	X	14
Mesenteric, lymphoma malignant lymphocytic								X																		1
Renal, leukemia mononuclear																								X		2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	36
Leukemia mononuclear																								X		2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X					X	X						X					X	X	17
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma adenosquamous, metastatic, lung																										1
Leukemia mononuclear												X												X		6
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																				X						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma													X													2
Thoracic, subcutaneous tissue, fibroma																X										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma adenosquamous																										1
Leukemia monocytic																			X							1
Leukemia mononuclear							X					X	X											X	X	16
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma adenosquamous, metastatic, lung																										1
Leukemia mononuclear																								X		3
SPECIAL SENSES SYSTEM																										
Eye																						+				2
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																								X		3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X												X		5
Sarcoma											X															1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 600 ppm

WEEKS ON STUDY	005	041	069	082	082	083	088	089	090	090	096	098	098	099	099	100	100	100	102	102	102	104	105	105	105
CARCASS ID	1691	1221	1331	1411	1391	1431	1731	1361	1351	1231	1471	1211	1701	1291	1251	1401	1531	1551	1441	1451	1711	1791	1311	1461	1511
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X		X							X			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X													X			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X							X			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Histiocytic sarcoma, metastatic												X													
Leukemia mononuclear			X		X		X	X	X		X		X		X	X	X	X	X			X	X		
Mesentery	+						+																		
Leukemia mononuclear							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X		X		X		X							X	X		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X		X				X				X							X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X				X							X			
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X	X		X				X		X	X	X			X	X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrosarcoma, metastatic, skin										X															
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Leukemia mononuclear			X				X		X		X		X		X		X	X	X			X	X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X		X		X		X		X		X	X	X			X	X		
Pheochromocytoma malignant																							X		
Pheochromocytoma, NOS											X					X			X			X			
Bilateral, pheochromocytoma, NOS																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X	X	X		X	X	X	X					X	X			X		X
Pars distalis, leukemia mononuclear							X								X							X			
Pars intermedia, leukemia mononuclear															X										
Pars nervosa, leukemia mononuclear															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X								X										
C-cell, adenoma													X				X								
C-cell, carcinoma																									
Follicle, adenoma																				X					
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear			X												X							X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X						X										
Seminal vesicle		+		+																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X							X			
Bilateral, interstitial cell, adenoma										X	X		X							X	X			X	X
Interstitial cell, adenoma				X										X	X	X			X			X	X		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	1521	1261	1341	1591	1661	1781	1241	1381	1561	1581	1601	1671	1281	1421	1491	1611	1631	1801	1301	1371	1481	1501	1541	1641	1761	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X										3
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X																	1
Hepatocellular adenoma		X										X														2
Histiocytic sarcoma, metastatic																										1
Leukemia mononuclear	X			X			X				X	X		X	X	X				X			X		X	25
Mesentery																										2
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										7
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X							X			7
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X												X				X			X		X	17
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrosarcoma, metastatic, skin																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear	X			X			X									X							X			16
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X			X									X							X			16
Pheochromocytoma malignant																										1
Pheochromocytoma, NOS											X				X			X								7
Bilateral, pheochromocytoma, NOS																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		2
Parathyroid gland	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X				X	X			X				X	X	X					X		24
Pars distalis, leukemia mononuclear																X							X			5
Pars intermedia, leukemia mononuclear																										1
Pars nervosa, leukemia mononuclear																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
C-cell, adenoma					X		X			X		X			X											7
C cell, carcinoma		X																								1
Follicle, adenoma							X																			2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Leukemia mononuclear																										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																							X			3
Seminal vesicle	+					+												+								5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Bilateral, interstitial cell, adenoma	X	X	X	X		X	X		X	X	X	X		X	X	X	X			X	X	X	X	X	X	27
Interstitial cell, adenoma								X										X								9

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	005	041	069	082	082	083	088	089	090	090	096	098	098	099	099	100	100	100	102	102	102	104	105	105	105
CARCASS ID	1691	1221	1331	1411	1391	1431	1731	1361	1351	1231	1471	1211	1701	1291	1251	1401	1531	1551	1441	1451	1711	1791	1311	1461	1511
HEMATOPOIETIC SYSTEM																									
Blood									+																
Leukemia mononuclear									X																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X	X		X		X		X	X			X			X	X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin										X															
Iliac, leukemia mononuclear																							X		
Mediastinal, leukemia mononuclear					X			X	X								X								
Mesenteric, leukemia mononuclear			X		X		X	X	X		X		X		X	X	X	X				X	X		
Renal, carcinoma, metastatic, kidney																			X						
Lymph node, mandibular	M	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X				X		X	X	X			X	X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Leukemia mononuclear			X		X		X	X	X		X		X		X	X	X	X	X			X	X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Carcinoma, metastatic, kidney																			X						
Leukemia mononuclear			X				X		X		X				X		X					X			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic												X													
Keratoacanthoma																									
Subcutaneous tissue, fibrosarcoma										X															
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X					X		X							X			
Cerebrum, astrocytoma malignant																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, kidney																			X						
Fibrosarcoma, metastatic, skin										X															
Histiocytic sarcoma, metastatic												X													
Leukemia mononuclear			X		X		X	X	X		X		X		X	X	X	X				X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X				X		X						X		
SPECIAL SENSES SYSTEM																									
Zymbal gland																+									
Carcinoma																X									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic												X													
Leukemia mononuclear			X				X	X	X		X		X		X							X			
Capsule, fibrosarcoma, metastatic, skin										X															
Renal tubule, adenoma																									
Transitional epithelium, carcinoma																			X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin										X															
Leukemia mononuclear							X	X			X				X			X				X	X		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	1521	1261	1341	1591	1661	1781	1241	1381	1561	1581	1601	1671	1281	1421	1491	1611	1631	1801	1301	1371	1481	1501	1541	1641	1761	
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X							X		X							X			15
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Iliac, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear																X										5
Mesenteric, leukemia mononuclear	X			X										X		X				X			X		X	20
Renal, carcinoma, metastatic, kidney																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																X				X			X			11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Leukemia mononuclear	X			X		X	X					X		X	X	X				X			X		X	25
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	46
Carcinoma, metastatic, kidney																										1
Leukemia mononuclear																X							X			9
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																										1
Keratoacanthoma			X																							1
Subcutaneous tissue, fibrosarcoma								X																		2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																							X			7
Cerebrum, astrocytoma malignant															X											1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma					X																					1
Carcinoma, metastatic, kidney																										1
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma, metastatic																										1
Leukemia mononuclear	X			X			X				X			X	X	X				X			X			22
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
SPECIAL SENSES SYSTEM																										
Zymbal gland							+																			2
Carcinoma							X																			2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic																										1
Leukemia mononuclear																X							X			10
Capsule, fibrosarcoma, metastatic, skin																										1
Renal tubule, adenoma								X																		1
Transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Leukemia mononuclear				X												X							X			10

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 1,200 ppm

WEEKS ON STUDY	030	069	071	078	078	080	080	080	086	086	086	087	089	091	091	092	094	095	096	098	098	099	101	102	103
CARCASS ID	2961	2871	2911	2471	2481	2841	2701	2811	2491	2621	2721	2571	2941	2711	2551	2971	2611	2651	2631	2581	2991	2431	2751	2831	2851
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X								
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X			X		X					X	X	X		X			X	X	
Serosa, mesothelioma malignant		X																							
Mesentery																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X														X								
Mesothelioma malignant		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Serosa, mesothelioma malignant		X																							
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X							X	X								
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X			X							X	X							X	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, mesothelioma malignant		X																							
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X				X		X						X			X			X	X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X				X		X						X			X			X	X	
Pheochromocytoma, NOS																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma														X											
Parathyroid gland	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X		X	X		X		X		X	X			X			X		X		X
Pars distalis, carcinoma													X												
Pars distalis, leukemia monocytic																							X		
Pars distalis, leukemia mononuclear			X																	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X					X	X							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X			X		X						X	X	X	X		X			X
Interstitial cell, adenoma			X	X			X			X					X	X							X	X	
Serosa, mesothelioma malignant		X																							

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	2461	2601	2691	2541	2741	2771	2891	2981	2531	2731	2921	2421	2561	2591	2901	2931	2441	2501	2511	2521	2821	2411	2761	2801	2881	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X				X	X							X			X	X			X			19
Serosa, mesothelioma malignant																										1
Mesentery								+												+	+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																			X							3
Mesothelioma malignant																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Serosa, mesothelioma malignant																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										3
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, mesothelioma malignant																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																	X							10
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																	X							10
Pheochromocytoma, NOS			X		X				X									X				X				6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X						X						X			X						18
Pars distalis, carcinoma																										1
Pars distalis, leukemia monocytic																										1
Pars distalis, leukemia mononuclear																			X							3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma						X				X				X					X				X			8
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	30
Interstitial cell, adenoma		X			X																					10
Serosa, mesothelioma malignant																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	030	069	071	078	078	080	080	080	086	086	086	087	089	091	091	092	094	095	096	098	098	099	101	102	103
CARCASS ID	2961	2871	2911	2471	2481	2841	2701	2811	2491	2621	2721	2571	2941	2711	2551	2971	2611	2651	2631	2581	2991	2431	2751	2831	2851
HEMATOPOIETIC SYSTEM																									
Blood				+		+										+									
Leukemia mononuclear						X										X									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X			X		X					X	X	X		X			X	X	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X						X								
Mediastinal, leukemia mononuclear																								X	
Mesenteric, leukemia mononuclear			X		X	X			X		X					X	X	X		X			X	X	
Lymph node, mandibular	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X	X						X	X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X			X		X					X	X	X		X			X	X	
Lymphoma malignant						X																			
Capsule, mesothelioma malignant		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M
Leukemia mononuclear			X		X	X			X																
Osteosarcoma, metastatic, uncertain primary site																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma											X														
Subcutaneous tissue, fibrosarcoma																									
Tail, papilloma squamous																			X						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Fibrosarcoma	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X																				
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma adenosquamous												X													
Fibrous histiocytoma, metastatic, skin																									
Leukemia mononuclear			X		X	X			X		X					X	X	X		X			X	X	
Osteosarcoma, metastatic, uncertain primary site																			X						
Nose	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Zymbal gland																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X						X						X		
Capsule, mesothelioma malignant		X																							
Renal tubule, adenoma																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X														X		
Serosa, mesothelioma malignant		X																							
Transitional epithelium, papilloma																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	2461	2601	2691	2541	2741	2771	2891	2981	2531	2731	2921	2421	2561	2591	2901	2931	2441	2501	2511	2521	2821	2411	2761	2801	2881	
HEMATOPOIETIC SYSTEM																										
Blood			+																							4
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								12
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Mediastinal, leukemia mononuclear																										1
Mesenteric, leukemia mononuclear		X							X							X			X	X			X			17
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Leukemia mononuclear																										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X				X	X							X			X	X			X			19
Lymphoma malignant																										1
Capsule, mesothelioma malignant																										1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear																										4
Osteosarcoma, metastatic, uncertain primary site																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma										X																1
Tail, papilloma squamous																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								3
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma adenosquamous																										1
Fibrous histiocytoma, metastatic, skin			X																							1
Leukemia mononuclear		X																	X	X						14
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye				+											+											2
Zymbal gland			+																							1
Carcinoma			X																							1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								4
Capsule, mesothelioma malignant																										1
Renal tubule, adenoma																			X							2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								3
Serosa, mesothelioma malignant																										1
Transitional epithelium, papilloma												X														1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	7/49 (14%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	21.6%	23.2%	24.6%
Terminal Rates (c)	5/29 (17%)	3/28 (11%)	4/22 (18%)
Day of First Observation	618	670	715
Life Table Tests (d)	P=0.507	P=0.516	P=0.558
Logistic Regression Tests (d)	P=0.487N	P=0.548	P=0.552N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.517	P=0.484N
Adrenal Gland Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	7/49 (14%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	21.6%	26.3%	24.6%
Terminal Rates (c)	5/29 (17%)	4/28 (14%)	4/22 (18%)
Day of First Observation	618	670	715
Life Table Tests (d)	P=0.497	P=0.410	P=0.558
Logistic Regression Tests (d)	P=0.491N	P=0.442	P=0.552N
Cochran-Armitage Trend Test (d)	P=0.427N		
Fisher Exact Test (d)		P=0.410	P=0.484N
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8.8%	7.1%	10.4%
Terminal Rates (c)	2/30 (7%)	2/28 (7%)	1/22 (5%)
Day of First Observation	618	729	632
Life Table Tests (d)	P=0.487	P=0.525N	P=0.571
Logistic Regression Tests (d)	P=0.568	P=0.488N	P=0.649
Cochran-Armitage Trend Test (d)	P=0.588N		
Fisher Exact Test (d)		P=0.500N	P=0.661N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	12.4%	7.1%	0.0%
Terminal Rates (c)	3/30 (10%)	2/28 (7%)	0/22 (0%)
Day of First Observation	652	729	
Life Table Tests (d)	P=0.061N	P=0.358N	P=0.101N
Logistic Regression Tests (d)	P=0.042N	P=0.315N	P=0.072N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.339N	P=0.059N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	12.4%	10.7%	0.0%
Terminal Rates (c)	3/30 (10%)	3/28 (11%)	0/22 (0%)
Day of First Observation	652	729	
Life Table Tests (d)	P=0.081N	P=0.526N	P=0.101N
Logistic Regression Tests (d)	P=0.056N	P=0.473N	P=0.072N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.059N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	22/49 (45%)	24/50 (48%)	18/50 (36%)
Adjusted Rates (b)	52.4%	59.7%	45.0%
Terminal Rates (c)	11/30 (37%)	13/28 (46%)	4/22 (18%)
Day of First Observation	473	572	478
Life Table Tests (d)	P=0.513N	P=0.429	P=0.511N
Logistic Regression Tests (d)	P=0.212N	P=0.455	P=0.221N
Cochran-Armitage Trend Test (d)	P=0.212N		
Fisher Exact Test (d)		P=0.457	P=0.243N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	22/49 (45%)	24/50 (48%)	19/50 (38%)
Adjusted Rates (b)	52.4%	59.7%	46.4%
Terminal Rates (c)	11/30 (37%)	13/28 (46%)	4/22 (18%)
Day of First Observation	473	572	478
Life Table Tests (d)	P=0.484	P=0.429	P=0.551
Logistic Regression Tests (d)	P=0.274N	P=0.455	P=0.284N
Cochran-Armitage Trend Test (d)	P=0.276N		
Fisher Exact Test (d)		P=0.457	P=0.311N
Subcutaneous Tissue: Fibroma			
Overall Rates (e)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.9%	0.0%	2.4%
Terminal Rates (c)	2/30 (7%)	0/28 (0%)	0/22 (0%)
Day of First Observation	625		597
Life Table Tests (d)	P=0.221N	P=0.131N	P=0.382N
Logistic Regression Tests (d)	P=0.175N	P=0.119N	P=0.304N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (e)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	8.9%	5.9%	6.9%
Terminal Rates (c)	2/30 (7%)	1/28 (4%)	1/22 (5%)
Day of First Observation	625	625	597
Life Table Tests (d)	P=0.500N	P=0.519N	P=0.601N
Logistic Regression Tests (d)	P=0.410N	P=0.499N	P=0.508N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	36/50 (72%)	36/50 (72%)	40/50 (80%)
Adjusted Rates (b)	94.6%	92.2%	95.1%
Terminal Rates (c)	28/30 (93%)	25/28 (89%)	20/22 (91%)
Day of First Observation	614	570	495
Life Table Tests (d)	P=0.013	P=0.488	P=0.019
Logistic Regression Tests (d)	P=0.072	P=0.435N	P=0.096
Cochran-Armitage Trend Test (d)	P=0.210		
Fisher Exact Test (d)		P=0.588N	P=0.241
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	8/50 (16%)
Adjusted Rates (b)	15.2%	22.3%	29.1%
Terminal Rates (c)	4/30 (13%)	5/28 (18%)	5/22 (23%)
Day of First Observation	589	686	606
Life Table Tests (d)	P=0.113	P=0.360	P=0.145
Logistic Regression Tests (d)	P=0.194	P=0.404	P=0.245
Cochran-Armitage Trend Test (d)	P=0.231		
Fisher Exact Test (d)		P=0.380	P=0.277
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	15.2%	25.7%	29.1%
Terminal Rates (c)	4/30 (13%)	6/28 (21%)	5/22 (23%)
Day of First Observation	589	686	606
Life Table Tests (d)	P=0.111	P=0.257	P=0.145
Logistic Regression Tests (d)	P=0.195	P=0.300	P=0.245
Cochran-Armitage Trend Test (d)	P=0.236		
Fisher Exact Test (d)		P=0.277	P=0.277

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	17/50 (34%)	26/50 (52%)	19/50 (38%)
Adjusted Rates (b)	41.3%	62.3%	52.1%
Terminal Rates (c)	8/30 (27%)	13/28 (46%)	7/22 (32%)
Day of First Observation	416	478	495
Life Table Tests (d)	P=0.184	P=0.085	P=0.231
Logistic Regression Tests (d)	P=0.374	P=0.053	P=0.429
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.053	P=0.418

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

TABLE A4. HISTORICAL INCIDENCE OF KIDNEY TUBULAR CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas or Carcinomas in Controls
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories	
Propylene oxide	0/50
Methyl methacrylate	0/50
Propylene	0/50
1,2-Epoxybutane	0/50
Dichloromethane	0/50
Tetrachloroethylene	(b) 1/49
Bromoethane	0/47
TOTAL	1/346 (0.3%)
SD (c)	0.77%
Range (d)	
High	1/49
Low	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	(e) 14/1,590 (0.9%)
SD (c)	1.68%
Range (d)	
High	3/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Tubular cell adenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 10 tubular cell adenomas, 1 adenoma, NOS, 2 tubular cell adenocarcinomas, and 1 tubular adenocarcinoma

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(50)	(50)	(49)
Erosion		1 (2%)	
Hemorrhage		2 (4%)	
Inflammation, acute	1 (2%)		
Intestine large, colon	(50)	(50)	(49)
Granuloma			1 (2%)
Parasite metazoan	2 (4%)	4 (8%)	1 (2%)
Intestine large, rectum	(49)	(50)	(49)
Erosion		1 (2%)	
Inflammation, acute			1 (2%)
Parasite metazoan	2 (4%)	4 (8%)	7 (14%)
Ulcer		4 (8%)	3 (6%)
Intestine small, duodenum	(50)	(50)	(49)
Erosion			1 (2%)
Ulcer	1 (2%)		
Intestine small, ileum	(49)	(50)	(49)
Erosion			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis	7 (14%)	11 (22%)	3 (6%)
Congestion	3 (6%)	2 (4%)	1 (2%)
Developmental malformation	1 (2%)	4 (8%)	2 (4%)
Fatty change	3 (6%)	2 (4%)	8 (16%)
Focal cellular change	28 (56%)	23 (46%)	23 (46%)
Granuloma	1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation		2 (4%)	
Hemorrhage		2 (4%)	
Necrosis	2 (4%)	2 (4%)	1 (2%)
Bile duct, dilatation		1 (2%)	
Bile duct, hyperplasia	48 (96%)	49 (98%)	49 (98%)
Bile duct, inflammation, chronic		1 (2%)	
Portal, inflammation, chronic	48 (96%)	45 (90%)	46 (92%)
Serosa, fibrosis			1 (2%)
Mesentery	(2)	(2)	(4)
Inflammation, acute		1 (50%)	
Arteriole, inflammation, chronic			2 (50%)
Arteriole, inflammation, chronic active			1 (25%)
Fat, necrosis	2 (100%)		1 (25%)
Pancreas	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Acinus, atrophy	30 (60%)	34 (68%)	30 (60%)
Acinus, hyperplasia	1 (2%)	4 (8%)	1 (2%)
Arteriole, inflammation, chronic active			1 (2%)
Arteriole, mineralization			1 (2%)
Artery, inflammation, chronic	1 (2%)		
Salivary glands	(50)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)	
Acinus, atrophy		1 (2%)	1 (2%)
Arteriole, mineralization			1 (2%)
Stomach	(50)	(50)	(50)
Ulcer			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(50)	(50)	(49)
Cyst	1 (2%)		
Erosion	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, squamous	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute	4 (8%)	3 (6%)	2 (4%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic active	3 (6%)	2 (4%)	2 (4%)
Mineralization			1 (2%)
Ulcer	4 (8%)	7 (14%)	9 (18%)
Stomach, glandular	(50)	(50)	(49)
Inflammation, acute	1 (2%)		
Inflammation, chronic active			1 (2%)
Mineralization			2 (4%)
Mucosa, congestion		1 (2%)	
Mucosa, dilatation	17 (34%)	21 (42%)	18 (37%)
Mucosa, ectasia	2 (4%)		
Mucosa, erosion	4 (8%)	11 (22%)	9 (18%)
Mucosa, granuloma		1 (2%)	
Mucosa, hemorrhage		1 (2%)	
Mucosa, inflammation, acute		1 (2%)	
Mucosa, ulcer	2 (4%)	5 (10%)	3 (6%)
CARDIOVASCULAR SYSTEM			
Blood vessel	(50)	(50)	(50)
Aorta, mineralization			1 (2%)
Thoracic, inflammation, chronic active			1 (2%)
Heart	(50)	(50)	(50)
Cardiomyopathy, chronic	49 (98%)	47 (94%)	47 (94%)
Hemorrhage		1 (2%)	
Mineralization			1 (2%)
Artery, mineralization			1 (2%)
Atrium, thrombus		6 (12%)	3 (6%)
Pericardium, inflammation, chronic		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Degeneration, fatty	35 (70%)	41 (82%)	43 (86%)
Hyperplasia	15 (30%)	10 (20%)	11 (22%)
Hypertrophy	4 (8%)	5 (10%)	3 (6%)
Pigmentation	43 (86%)	46 (92%)	39 (78%)
Adrenal gland, medulla	(49)	(50)	(50)
Hyperplasia	10 (20%)	15 (30%)	4 (8%)
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	1 (2%)	4 (8%)	3 (6%)
Parathyroid gland	(42)	(45)	(44)
Hyperplasia	2 (5%)	1 (2%)	1 (2%)
Hypertrophy		2 (4%)	
Pituitary gland	(49)	(50)	(50)
Pars distalis, angiectasis		3 (6%)	1 (2%)
Pars distalis, atrophy	1 (2%)		
Pars distalis, cyst	3 (6%)	6 (12%)	5 (10%)
Pars distalis, hemorrhage	1 (2%)		1 (2%)
Pars distalis, hyperplasia	18 (37%)	22 (44%)	11 (22%)
Pars intermedia, angiectasis		2 (4%)	1 (2%)
Pars intermedia, cyst	2 (4%)	2 (4%)	1 (2%)
Pars intermedia, hyperplasia		2 (4%)	
Pars nervosa, pigmentation	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(50)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)		1 (2%)
Ultimobranchial cyst	1 (2%)		2 (4%)
C-cell, hyperplasia	12 (24%)	20 (40%)	14 (28%)
Follicle, ectasia	3 (6%)	2 (4%)	3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Preputial gland	(50)	(50)	(50)
Abscess	3 (6%)		
Hyperplasia		1 (2%)	1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	29 (58%)	28 (56%)	22 (44%)
Inflammation, chronic active	10 (20%)	17 (34%)	25 (50%)
Mineralization			1 (2%)
Duct, ectasia	1 (2%)		2 (4%)
Prostate	(50)	(50)	(50)
Atrophy	1 (2%)		
Hyperplasia	10 (20%)	3 (6%)	3 (6%)
Inflammation, acute	7 (14%)	7 (14%)	5 (10%)
Inflammation, chronic	1 (2%)	3 (6%)	2 (4%)
Inflammation, chronic active	14 (28%)	6 (12%)	10 (20%)
Seminal vesicle		(5)	
Dilatation		1 (20%)	
Testes	(50)	(50)	(50)
Atrophy	11 (22%)	12 (24%)	9 (18%)
Congestion		1 (2%)	
Mineralization		2 (4%)	
Arteriole, inflammation, chronic		2 (4%)	1 (2%)
Interstitial cell, hyperplasia	35 (70%)	46 (92%)	37 (74%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Myelofibrosis	3 (6%)	1 (2%)	5 (10%)
Lymph node	(50)	(50)	(50)
Congestion		1 (2%)	
Edema	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Mediastinal, congestion	1 (2%)	5 (10%)	
Mediastinal, hemorrhage			1 (2%)
Mediastinal, hyperplasia, lymphoid		1 (2%)	1 (2%)
Mesenteric, congestion	1 (2%)	1 (2%)	4 (8%)
Mesenteric, hyperplasia, lymphoid	17 (34%)	20 (40%)	22 (44%)
Mesenteric, inflammation, acute		1 (2%)	
Popliteal, hyperplasia, lymphoid			1 (2%)
Lymph node, mandibular	(36)	(45)	(37)
Congestion	10 (28%)	10 (22%)	3 (8%)
Cyst	1 (3%)	1 (2%)	1 (3%)
Hyperplasia, lymphoid	32 (89%)	31 (69%)	30 (81%)
Spleen	(50)	(50)	(50)
Fibrosis	5 (10%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	42 (84%)	42 (84%)	40 (80%)
Hyperplasia, lymphoid	2 (4%)		3 (6%)
Infarct		1 (2%)	
Mineralization	1 (2%)		
Pigmentation	39 (78%)	37 (74%)	42 (84%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(44)	(46)	(46)
Congestion	2 (5%)	5 (11%)	1 (2%)
Cyst	4 (9%)	1 (2%)	
Hyperplasia, lymphoid		4 (9%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(48)	(49)
Inflammation, acute	2 (4%)		
Inflammation, chronic	1 (2%)		
Acinus, ectasia	34 (68%)	25 (52%)	28 (57%)
Duct, ectasia	10 (20%)	19 (40%)	8 (16%)
Skin	(50)	(50)	(50)
Abscess		1 (2%)	1 (2%)
Cyst epithelial inclusion	1 (2%)	2 (4%)	
Epidermis, cyst	1 (2%)		
Foot, ulcer			1 (2%)
Hair follicle, inflammation, chronic		1 (2%)	
Hair follicle, head, hemorrhage	1 (2%)		
Hair follicle, head, inflammation, acute	1 (2%)		
Head, abscess			1 (2%)
Head, inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Head, inflammation, chronic active	1 (2%)		
Subcutaneous tissue, edema		1 (2%)	
Subcutaneous tissue, hemorrhage		1 (2%)	
Tail, inflammation, chronic active	1 (2%)		
Tail, subcutaneous tissue, inflammation, acute			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, abscess		1 (2%)	
Cranium, fibrous osteodystrophy	1 (2%)	1 (2%)	2 (4%)
Cranium, inflammation, chronic			1 (2%)
Femur, fibrous osteodystrophy	1 (2%)	4 (8%)	2 (4%)
Humerus, fracture			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	5 (10%)	7 (14%)	6 (12%)
Hemorrhage	11 (22%)	8 (16%)	2 (4%)
Necrosis	1 (2%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	6 (12%)	3 (6%)	4 (8%)
Hemorrhage	8 (16%)	4 (8%)	5 (10%)
Infiltration cellular, lymphocytic	50 (100%)	47 (94%)	49 (98%)
Inflammation, chronic			1 (2%)
Metaplasia, osseous			1 (2%)
Pigmentation, cholesterol	1 (2%)	2 (4%)	2 (4%)
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	3 (6%)
Alveolus, infiltration cellular, histiocytic	26 (52%)	18 (36%)	25 (50%)
Alveolus, mineralization			2 (4%)
Arteriole, mineralization	41 (82%)	40 (80%)	38 (76%)
Bronchiole, inflammation, acute			2 (4%)
Bronchiole, mineralization	1 (2%)		
Interstitium, inflammation, chronic	5 (10%)	6 (12%)	10 (20%)
Interstitium, inflammation, chronic active	5 (10%)		2 (4%)
Peribronchiolar, inflammation, chronic		3 (6%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
RESPIRATORY SYSTEM			
Lung (Continued)	(50)	(50)	(50)
Peribronchiolar, inflammation, chronic active		1 (2%)	
Pleura, inflammation, chronic active	1 (2%)		
Nose	(50)	(50)	(49)
Inflammation, chronic active	1 (2%)		
Lumen, degeneration			1 (2%)
Lumen, foreign body	4 (8%)	5 (10%)	2 (4%)
Lumen, hemorrhage	31 (62%)	25 (50%)	35 (71%)
Mucosa, hemorrhage		1 (2%)	
Mucosa, inflammation, acute	30 (60%)	30 (60%)	40 (82%)
Mucosa, inflammation, chronic active	1 (2%)		
Nasolacrimal duct, degeneration		1 (2%)	
Nasolacrimal duct, inflammation	1 (2%)		
Nasolacrimal duct, inflammation, acute	4 (8%)	1 (2%)	2 (4%)
Nasopharyngeal duct, inflammation, acute	1 (2%)		
Olfactory epithelium, degeneration	39 (78%)	48 (96%)	42 (86%)
Olfactory epithelium, erosion		3 (6%)	8 (16%)
Olfactory epithelium, metaplasia		1 (2%)	1 (2%)
Olfactory epithelium, metaplasia, squamous			2 (4%)
Respiratory epithelium, degeneration	15 (30%)	37 (74%)	31 (63%)
Respiratory epithelium, erosion	4 (8%)	6 (12%)	3 (6%)
Respiratory epithelium, hemorrhage		1 (2%)	
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)	
Respiratory epithelium, ulcer			1 (2%)
Vomeronasal organ, inflammation, acute	1 (2%)		1 (2%)
Trachea	(50)	(50)	(50)
Inflammation, acute		1 (2%)	3 (6%)
Inflammation, chronic active		3 (6%)	1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(2)		(2)
Cataract	1 (50%)		2 (100%)
Retina, degeneration	1 (50%)		1 (50%)
Sclera, mineralization	1 (50%)		2 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Congestion		1 (2%)	
Infarct			2 (4%)
Infiltration cellular, lymphocytic	1 (2%)		
Mineralization			1 (2%)
Nephropathy, chronic	49 (98%)	48 (96%)	48 (96%)
Pelvis, inflammation, acute		1 (2%)	1 (2%)
Renal tubule, cyst	1 (2%)	2 (4%)	5 (10%)
Renal tubule, hyperplasia	4 (8%)	4 (8%)	
Renal tubule, pigmentation	50 (100%)	48 (96%)	47 (94%)
Urinary bladder	(50)	(50)	(50)
Calculus gross observation	1 (2%)		
Calculus micro observation only		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)
Transitional epithelium, hyperplasia		1 (2%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(50)	(49)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Intestine small, duodenum	(50)	(49)	(49)
Leukemia mononuclear		2 (4%)	
Intestine small, ileum	(50)	(49)	(49)
Leukemia mononuclear		2 (4%)	
Intestine small, jejunum	(50)	(49)	(49)
Leukemia mononuclear		1 (2%)	
Liver	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)	3 (6%)	
Leukemia mononuclear	17 (34%)	16 (32%)	10 (20%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear			1 (2%)
Pancreas	(50)	(49)	(50)
Leukemia mononuclear	3 (6%)		1 (2%)
Salivary glands	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	3 (6%)
Papilloma squamous			1 (2%)
Squamous cell carcinoma			1 (2%)
Stomach, glandular	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	2 (4%)	3 (6%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	5 (10%)	4 (8%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(49)
Leukemia mononuclear	14 (28%)	9 (18%)	4 (8%)
Adrenal gland, medulla	(49)	(48)	(49)
Leukemia mononuclear	10 (20%)	6 (13%)	3 (6%)
Pheochromocytoma, NOS	1 (2%)		4 (8%)
Islets, pancreatic	(50)	(49)	(50)
Carcinoma		2 (4%)	1 (2%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	31 (62%)	27 (54%)	31 (62%)
Pars distalis, craniopharyngioma		1 (2%)	
Pars distalis, leukemia mononuclear	3 (6%)		2 (4%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)		
C-cell, adenoma	2 (4%)	8 (16%)	3 (6%)
C-cell, carcinoma	2 (4%)	2 (4%)	2 (4%)
GENERAL BODY SYSTEM			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
GENITAL SYSTEM			
Clitoral gland	(49)	(50)	(44)
Adenoma	2 (4%)	4 (8%)	3 (7%)
Ovary	(50)	(50)	(50)
Granulosa cell tumor malignant			2 (4%)
Leukemia mononuclear	4 (8%)	3 (6%)	2 (4%)
Uterus	(50)	(50)	(50)
Adenocarcinoma			1 (2%)
Adenoma	1 (2%)		
Leukemia mononuclear	3 (6%)	1 (2%)	2 (4%)
Endometrium, polyp stromal	4 (8%)	5 (10%)	2 (4%)
Endometrium, sarcoma stromal	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Bone marrow	(49)	(50)	(50)
Leukemia mononuclear	5 (10%)	4 (8%)	2 (4%)
Lymph node	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	
Mediastinal, leukemia mononuclear	1 (2%)	2 (4%)	
Mediastinal, lymphoma malignant histiocytic		1 (2%)	
Mesenteric, leukemia mononuclear	15 (30%)	14 (28%)	8 (16%)
Lymph node, mandibular	(47)	(48)	(42)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Leukemia mononuclear	3 (6%)	5 (10%)	1 (2%)
Spleen	(50)	(50)	(50)
Leukemia mononuclear	17 (34%)	16 (32%)	10 (20%)
Thymus	(46)	(46)	(46)
Leukemia mononuclear	6 (13%)	5 (11%)	2 (4%)
Thymoma benign	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Adenocarcinoma	2 (4%)	1 (2%)	6 (12%)
Adenoma	2 (4%)	1 (2%)	1 (2%)
Fibroadenoma	13 (26%)	4 (8%)	7 (14%)
Skin	(50)	(50)	(50)
Keratoacanthoma			1 (2%)
Subcutaneous tissue, fibroma			1 (2%)
Subcutaneous tissue, lipoma			1 (2%)
Subcutaneous tissue, neurofibrosarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Astrocytoma malignant	1 (2%)		
Leukemia mononuclear	4 (8%)	2 (4%)	1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Leukemia mononuclear	16 (32%)	13 (26%)	6 (12%)
Nose	(49)	(50)	(50)
Mucosa, squamous cell carcinoma			1 (2%)
Trachea	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Eye	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Zymbal gland	*(50)	*(50)	*(50)
Carcinoma	1 (2%)		
Squamous cell carcinoma		1 (2%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	3 (6%)	4 (8%)	5 (10%)
Sarcoma			1 (2%)
Renal tubule, carcinoma			1 (2%)
Urinary bladder	(50)	(50)	(50)
Leukemia mononuclear	6 (12%)	2 (4%)	2 (4%)
Transitional epithelium, papilloma	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	18 (36%)	16 (32%)	10 (20%)
Lymphoma malignant histiocytic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	32	35	30
Interval sacrifice	10	10	10
Dead	7	7	6
Moribund	11	8	14
TUMOR SUMMARY			
Total animals with primary neoplasms **	46	43	43
Total primary neoplasms	86	77	84
Total animals with benign neoplasms	39	37	34
Total benign neoplasms	60	53	52
Total animals with malignant neoplasms	21	21	23
Total malignant neoplasms	25	24	28
Total animals with secondary neoplasms ***	1		
Total secondary neoplasms	4		
Total animals with neoplasms-- uncertain benign or malignant	1		4
Total uncertain neoplasms	1		4

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: CHAMBER CONTROL

WEEKS ON STUDY	062	071	082	084	090	092	092	092	092	094	097	097	100	102	102	103	104	105	105	105	105	105	105	105	105
CARCASS ID	0691	1121	1021	1111	0701	0801	0941	0861	0781	1161	0921	1041	0911	0741	0731	0791	1191	0681	0771	0811	0971	0981	1141	1181	0611
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Leukemia mononuclear		X			X		X			X	X		X				X	X	X			X			
Mesentery															+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X											X						X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X									X														
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X				X		X						X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X		X			X	X						X	X	X			X			
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X				X						X	X	X						
Pheochromocytoma, NOS																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X	X	X					X		X	X	X	X	X	X	X		X		X	X	X	X
Pars distalis, leukemia mononuclear											X						X								
Pars intermedia, adenoma																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
C-cell, adenoma										X															
C-cell, carcinoma								X																	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X								X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear							X				X														
Endometrium, polyp stromal											X														
Endometrium, sarcoma stromal																									
Vagina						+			+							+									

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	0651	0871	0901	0931	1201	0751	0851	0881	1001	1011	1071	1081	0621	0661	0711	0831	0951	1031	0641	0821	0841	0991	1061	1091	1151	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Carcinoma, metastatic, thyroid gland					X																					1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X															2
Leukemia mononuclear			X		X		X		X				X			X						X				17
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																					1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																					3
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X		X		X							X						X				14
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear					X		X		X							X										10
Pheochromocytoma, NOS																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X			X	X		X		X	X	X		X		X	X	X		X		31
Pars distalis, leukemia mononuclear					X																					3
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C-cell, adenoma																			X							2
C-cell, carcinoma					X																					2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																				X				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																					4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Leukemia mononuclear					X																					3
Endometrium, polyp stromal												X				X									X	4
Endometrium, sarcoma stromal	X																									1
Vagina					+																					4

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

WEEKS ON STUDY	062	071	082	084	090	092	092	092	092	094	097	097	100	102	102	103	104	105	105	105	105	105	105	105	105
CARCASS ID	0691	1121	1021	1111	0701	0801	0941	0861	0781	1161	0921	1041	0911	0741	0731	0791	1191	0681	0771	0811	0971	0981	1141	1181	0611
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X		X				X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mediastinal, leukemia mononuclear													X												
Mesenteric, leukemia mononuclear		X			X	X	X			X	X		X				X	X	X						
Lymph node, mandibular	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear						X					X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X			X	X		X				X	X	X						
Thymus	+	+	M	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X					X						X				X								
Thymoma benign																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Adenoma															X										X
Fibroadenoma										X					X		X			X		X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Leukemia mononuclear							X				X								X						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear		X			X	X	X			X	X						X	X	X			X			
Nose	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear																									
SPECIAL SENSES SYSTEM																									
Eye			+				+				+		+												
Leukemia mononuclear							X																		
Zymbal gland						+																			
Carcinoma						X																			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X				X		X				X								
Transitional epithelium, papilloma																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	0651	0871	0901	0931	1201	0751	0851	0881	1001	1011	1071	1081	0621	0661	0711	0831	0951	1131	0641	0821	0841	0991	1061	1091	1151	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear					X											X										5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			1
Mediastinal, leukemia mononuclear																										1
Mesenteric, leukemia mononuclear			X		X		X		X							X										15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, thyroid gland					X																					1
Leukemia mononuclear																X										3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X		X		X				X			X						X				17
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear					X											X										6
Thymoma benign							X																			1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X										2
Adenoma																										2
Fibroadenoma						X	X					X	X		X			X		X						13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant															X											1
Leukemia mononuclear					X																					4
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland					X																					1
Leukemia mononuclear			X		X		X		X							X						X				16
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland					X																					1
Leukemia mononuclear					X																					1
SPECIAL SENSES SYSTEM																										
Eye															+											5
Leukemia mononuclear																										1
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																					3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																	X				6
Transitional epithelium, papilloma													X													1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 600 ppm

WEEKS ON STUDY	060	066	077	078	079	080	094	094	094	097	097	098	098	102	103	105	105	105	105	105	105	105	105	105	105
CARCASS ID	2311	1821	2151	2331	1951	1921	2071	2081	2021	2191	2231	1811	2271	2201	2111	1851	1941	1961	2061	2131	2261	2281	1831	1931	2011
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X												X			
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X												X			
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Leukemia mononuclear				X			X			X		X		X	X					X	X	X			
Mesentery																							+		
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X										X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X										X			
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X		X		X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X		X		X							X	X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X		X		X							X	X			
Islets, pancreatic	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X				X	X	X		X		X	X	X			X	X	X	X		X
Pars distalis, craniopharyngioma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma					X			X	X								X	X			X				
C-cell, carcinoma																									X
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X								X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Endometrium, polyp stromal			X	X	X																X				
Vagina									+				+										+		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	2121	2161	2351	1981	1991	2031	2141	2221	2291	2321	1861	1881	1911	2171	2211	2241	2371	1841	1891	1971	2001	2091	2251	2391	2401	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X				X				X															3
Leukemia mononuclear			X			X		X	X		X		X		X											16
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Tooth														+												1
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear													X													4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear									X				X													9
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma		X	X																							2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X				X		X	X	X	X			X		X						X	X	X	X	27
Pars distalis, craniopharyngioma			X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X			X																		8
C-cell, carcinoma																					X					2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X	X						X															4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Endometrium, polyp stromal																							X			5
Vagina			+																							4

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	060	066	077	078	079	080	094	094	094	097	097	098	098	102	103	105	105	105	105	105	105	105	105	105	105
CARCASS ID	2311	1821	2151	2331	1951	1921	2071	2081	2021	2191	2231	1811	2271	2201	2111	1851	1941	1961	2061	2131	2261	2281	1831	1931	2011
HEMATOPOIETIC SYSTEM																									
Blood							+																		
Leukemia mononuclear							X																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X		X										X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X														X				
Mediastinal, leukemia mononuclear							X					X													
Mediastinal, lymphoma malignant histiocytic																									
Mesenteric, leukemia mononuclear				X						X		X		X	X						X	X			
Lymph node, mandibular	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X									X	X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X		X		X	X					X	X	X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Leukemia mononuclear															X							X			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma															X										
Fibroadenoma																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, neurofibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X															
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X			X		X		X							X	X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye															+								+		
Zymbal gland	+																								
Squamous cell carcinoma	X																								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X		X								X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X								X			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	2121	2161	2351	1981	1991	2031	2141	2221	2291	2321	1861	1881	1911	2171	2211	2241	2371	1841	1891	1971	2001	2091	2251	2391	2401	
HEMATOPOIETIC SYSTEM																										
Blood																										1
Leukemia mononuclear																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Mediastinal, leukemia mononuclear																										2
Mediastinal, lymphoma malignant histiocytic							X																			1
Mesenteric, leukemia mononuclear			X			X		X	X		X		X		X											14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear			X										X													5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X			X		X	X		X		X		X											16
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	46
Leukemia mononuclear			X										X		X											5
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															1
Adenoma																										1
Fibroadenoma																				X	X				X	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, neurofibrosarcoma															X											1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X			X			X		X		X		X											13
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye											+					+										4
Zymbal gland																										1
Squamous cell carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 1,200 ppm

WEEKS ON STUDY	0 2 4	0 6 1	0 8 1	0 8 1	0 8 1	0 8 4	0 8 7	0 8 7	0 9 0	0 9 2	0 9 3	0 9 3	0 9 4	0 9 4	0 9 6	0 9 7	0 9 9	1 0 1	1 0 2	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	3 0 6 1	3 3 5 1	3 2 6 1	3 0 4 1	3 2 8 1	3 3 1 1	3 1 8 1	3 4 8 1	3 5 6 1	3 0 9 1	3 1 3 1	3 1 6 1	3 4 1 1	3 5 2 1	3 4 2 1	3 0 2 1	3 0 5 1	3 4 7 1	3 2 0 1	3 3 3 1	3 0 1 1	3 1 9 1	3 4 4 1	3 4 6 1	3 5 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X		X			X	X									X		X
Mesentery										+															
Leukemia mononuclear										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X				X											
Papilloma squamous																									
Squamous cell carcinoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X				X											
Tooth																							+		+
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X					X	X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X							X	X											
Pheochromocytoma, NOS					X											X		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X					X			X	X	X	X	X	X	X	X	X		X	X		X
Pars distalis, leukemia mononuclear													X	X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					
C-cell, carcinoma																									X
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	M	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant													X												
Leukemia mononuclear										X				X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Leukemia mononuclear										X				X											
Endometrium, polyp stromal																									
Endometrium, sarcoma stromal			X																						
Vagina																	+		+						

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	3581	3101	3121	3221	3231	3361	3601	3031	3171	3241	3251	3371	3501	3141	3341	3381	3451	3491	3541	3111	3301	3401	3531	3571	3591	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X												X		10
Mesentery							+																			2
Leukemia mononuclear																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Papilloma squamous																						X				1
Squamous cell carcinoma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Tooth																										2
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										3
Pheochromocytoma, NOS																									X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X																							1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	M	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X				X		X	X				X	X			X	X		X	X	31
Pars distalis, leukemia mononuclear																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X																		X			3
C-cell, carcinoma						X																				2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma												X										X				3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																	X									2
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X										1
Leukemia mononuclear																										2
Endometrium, polyp stromal			X	X																						2
Endometrium, sarcoma stromal																										1
Vagina																						+				3

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	024	061	081	081	081	084	087	087	090	092	093	093	094	094	096	097	099	101	102	104	105	105	105	105	105
CARCASS ID	3061	3351	3261	3041	3281	3311	3181	3481	3561	3091	3131	3161	3411	3521	3421	3021	3051	3471	3201	3331	3011	3191	3441	3461	3551
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenteric, leukemia mononuclear						X		X		X			X	X									X		X
Lymph node, mandibular	+	+	M	M	M	M	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X		X			X	X									X		X
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Leukemia mononuclear													X	X											
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X														X				X	X		
Adenoma																									
Fibroadenoma			X								X										X	X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma		X																							
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma									X																
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X		X			X	X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye												+													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X		X			X	X											
Sarcoma																				X					
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X						X											

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	3581	3101	3121	3221	3231	3361	3601	3031	3171	3241	3251	3371	3501	3141	3341	3381	3451	3491	3541	3111	3301	3401	3531	3571	3591	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenteric, leukemia mononuclear																								X		8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Leukemia mononuclear																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X												X		10
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Leukemia mononuclear																										2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma	X																X									6
Adenoma																									X	1
Fibroadenoma						X							X													7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Subcutaneous tissue, fibroma																						X				1
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	49
Leukemia mononuclear																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, squamous cell carcinoma														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye		+																							+	3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
Sarcoma																										1
Renal tubule, carcinoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Adrenal Gland Medulla: Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	0/48 (0%)	4/49 (8%)
Adjusted Rates (b)	3.0%	0.0%	10.9%
Terminal Rates (c)	1/33 (3%)	0/34 (0%)	1/30 (3%)
Day of First Observation	729		564
Life Table Tests (d)	P=0.071	P=0.494N	P=0.157
Logistic Regression Tests (d)	P=0.086	P=0.494N	P=0.186
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.505N	P=0.181
Clitoral Gland: Adenoma			
Overall Rates (a)	2/49 (4%)	4/50 (8%)	3/44 (7%)
Adjusted Rates (b)	6.3%	10.6%	9.7%
Terminal Rates (c)	2/32 (6%)	3/35 (9%)	2/29 (7%)
Day of First Observation	729	554	706
Life Table Tests (d)	P=0.374	P=0.367	P=0.454
Logistic Regression Tests (d)	P=0.362	P=0.345	P=0.448
Cochran-Armitage Trend Test (d)	P=0.364		
Fisher Exact Test (d)		P=0.349	P=0.449
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.7%	8.6%	0.0%
Terminal Rates (c)	1/33 (3%)	3/35 (9%)	0/30 (0%)
Day of First Observation	710	729	
Life Table Tests (d)	P=0.226N	P=0.524	P=0.267N
Logistic Regression Tests (d)	P=0.226N	P=0.506	P=0.256N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	13/50 (26%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	35.8%	11.4%	20.4%
Terminal Rates (c)	10/33 (30%)	4/35 (11%)	5/30 (17%)
Day of First Observation	655	729	561
Life Table Tests (d)	P=0.094N	P=0.013N	P=0.158N
Logistic Regression Tests (d)	P=0.084N	P=0.014N	P=0.133N
Cochran-Armitage Trend Test (d)	P=0.067N		
Fisher Exact Test (d)		P=0.016N	P=0.105N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (e)	13/50 (26%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (b)	35.8%	13.9%	23.6%
Terminal Rates (c)	10/33 (30%)	4/35 (11%)	6/30 (20%)
Day of First Observation	655	717	561
Life Table Tests (d)	P=0.162N	P=0.028N	P=0.231N
Logistic Regression Tests (d)	P=0.146N	P=0.030N	P=0.203N
Cochran-Armitage Trend Test (d)	P=0.117N		
Fisher Exact Test (d)		P=0.033N	P=0.163N
Mammary Gland: Adenocarcinoma			
Overall Rates (e)	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	6.1%	2.9%	17.7%
Terminal Rates (c)	2/33 (6%)	1/35 (3%)	4/30 (13%)
Day of First Observation	729	729	563
Life Table Tests (d)	P=0.055	P=0.479N	P=0.110
Logistic Regression Tests (d)	P=0.061	P=0.479N	P=0.120
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.500N	P=0.134

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (e)	4/50 (8%)	2/50 (4%)	7/50 (14%)
Adjusted Rates (b)	11.6%	5.6%	20.9%
Terminal Rates (c)	3/33 (9%)	1/35 (3%)	5/30 (17%)
Day of First Observation	710	717	563
Life Table Tests (d)	P=0.151	P=0.317N	P=0.213
Logistic Regression Tests (d)	P=0.?	P=0.?	P=0.?
Cochran-Armitage Trend Test (d)	P=0.187		
Fisher Exact Test (d)		P=0.339N	P=0.262
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (e)	14/50 (28%)	6/50 (12%)	13/50 (26%)
Adjusted Rates (b)	38.6%	16.7%	36.6%
Terminal Rates (c)	11/33 (33%)	5/35 (14%)	9/30 (30%)
Day of First Observation	655	717	561
Life Table Tests (d)	P=0.546N	P=0.032N	P=0.568
Logistic Regression Tests (d)	P=0.515N	P=0.035N	P=0.565N
Cochran-Armitage Trend Test (d)	P=0.452N		
Fisher Exact Test (d)		P=0.039N	P=0.500N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	31/50 (62%)	27/50 (54%)	31/50 (62%)
Adjusted Rates (b)	70.1%	62.3%	71.8%
Terminal Rates (c)	20/33 (61%)	19/35 (54%)	18/30 (60%)
Day of First Observation	430	457	421
Life Table Tests (d)	P=0.362	P=0.243N	P=0.381
Logistic Regression Tests (d)	P=0.505	P=0.275N	P=0.540
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.272N	P=0.582N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	5.4%	20.0%	9.7%
Terminal Rates (c)	1/33 (3%)	5/35 (14%)	2/30 (7%)
Day of First Observation	655	553	723
Life Table Tests (d)	P=0.379	P=0.061	P=0.457
Logistic Regression Tests (d)	P=0.416	P=0.049	P=0.470
Cochran-Armitage Trend Test (d)	P=0.429		
Fisher Exact Test (d)		P=0.046	P=0.500
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	10.5%	25.3%	16.1%
Terminal Rates (c)	2/33 (6%)	7/35 (20%)	4/30 (13%)
Day of First Observation	642	553	723
Life Table Tests (d)	P=0.377	P=0.097	P=0.443
Logistic Regression Tests (d)	P=0.414	P=0.075	P=0.463
Cochran-Armitage Trend Test (d)	P=0.440		
Fisher Exact Test (d)		P=0.074	P=0.500
Uterus: Stromal Polyp			
Overall Rates (e)	4/50 (8%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	11.4%	11.6%	6.7%
Terminal Rates (c)	3/33 (9%)	2/35 (6%)	2/30 (7%)
Day of First Observation	675	537	729
Life Table Tests (d)	P=0.319N	P=0.517	P=0.387N
Logistic Regression Tests (d)	P=0.257N	P=0.526	P=0.378N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.500	P=0.339N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	18/50 (36%)	16/50 (32%)	10/50 (20%)
Adjusted Rates (b)	42.6%	38.6%	26.4%
Terminal Rates (c)	10/33 (30%)	10/35 (29%)	5/30 (17%)
Day of First Observation	491	540	584
Life Table Tests (d)	P=0.105N	P=0.376N	P=0.123N
Logistic Regression Tests (d)	P=0.051N	P=0.418N	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.050N		
Fisher Exact Test (d)		P=0.417N	P=0.059N

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

TABLE B4a. HISTORICAL INCIDENCE OF NOSE OR NASAL CAVITY SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories	
	0/349
Overall Historical Incidence for Untreated Controls in NTP Studies	
	0/1,643

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B4b. HISTORICAL INCIDENCE OF KIDNEY SARCOMAS OR TUBULAR CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas or Adenocarcinomas in Controls
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories	
Propylene oxide	(b) 1/50
Methyl methacrylate	0/50
Propylene	0/47
1,2-Epoxybutane	0/50
Dichloromethane	0/50
Tetrachloroethylene	0/50
Bromoethane	0/50
TOTAL	1/347 (0.3%)
SD (c)	0.76%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	(e) 2/1,639 (0.1%)
SD (c)	0.49%
Range (d)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Tubular cell adenocarcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one tubular cell adenoma and one adenocarcinoma, NOS; no renal sarcomas have been observed.

TABLE B4c. HISTORICAL INCIDENCE OF STOMACH SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories	
Propylene oxide	0/49
Methyl methacrylate	0/50
Propylene	0/48
1,2-Epoxybutane	0/50
Dichloromethane	0/50
Tetrachloroethylene	0/49
Bromoethane	0/48
TOTAL	0/344
SD (b)	0.00%
Range (c)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	(d) 3/1,623 (0.2%)
SD (b)	0.59%
Range (c)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two squamous cell papillomas and one squamous cell carcinoma

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	600 ppm	1,200 ppm
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(50)	(49)
Inflammation, chronic		1 (2%)	
Intestine large, cecum	(50)	(49)	(49)
Inflammation, acute	1 (2%)	2 (4%)	
Intestine large, colon	(50)	(49)	(49)
Inflammation, acute		1 (2%)	
Parasite metazoan	5 (10%)	1 (2%)	2 (4%)
Intestine large, rectum	(50)	(50)	(48)
Parasite metazoan	4 (8%)	5 (10%)	
Ulcer		1 (2%)	1 (2%)
Intestine small, duodenum	(50)	(49)	(49)
Edema		1 (2%)	
Erosion	1 (2%)	1 (2%)	1 (2%)
Intestine small, ileum	(50)	(49)	(49)
Edema		1 (2%)	
Ulcer		1 (2%)	
Intestine small, jejunum	(50)	(49)	(49)
Edema		1 (2%)	
Liver	(50)	(50)	(50)
Angiectasis	2 (4%)	6 (12%)	6 (12%)
Congestion		1 (2%)	
Developmental malformation	6 (12%)	5 (10%)	5 (10%)
Fatty change	3 (6%)	3 (6%)	2 (4%)
Focal cellular change	29 (58%)	41 (82%)	41 (82%)
Granuloma	12 (24%)	13 (26%)	10 (20%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)
Necrosis	4 (8%)	1 (2%)	
Arteriole, thrombus	1 (2%)		
Bile duct, hyperplasia	38 (76%)	36 (72%)	31 (62%)
Portal, hyperplasia			1 (2%)
Portal, inflammation, chronic	47 (94%)	46 (92%)	40 (80%)
Portal, inflammation, chronic active			1 (2%)
Venule, thrombus	1 (2%)		
Mesentery	(1)	(1)	(2)
Fat, necrosis	1 (100%)	1 (100%)	1 (50%)
Pancreas	(50)	(49)	(50)
Infiltration cellular, lymphocytic			1 (2%)
Inflammation, chronic active			1 (2%)
Acinus, atrophy	18 (36%)	24 (49%)	15 (30%)
Acinus, hyperplasia	1 (2%)	4 (8%)	
Acinus, vacuolization cytoplasmic			1 (2%)
Arteriole, inflammation, chronic			1 (2%)
Duct, ectasia	1 (2%)		
Salivary glands	(50)	(50)	(50)
Infiltration cellular, lymphocytic			1 (2%)
Acinus, atrophy			1 (2%)
Stomach	(50)	(50)	(50)
Foreign body			1 (2%)
Hyperplasia, squamous			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
Hyperplasia, squamous	1 (2%)	2 (4%)	3 (6%)
Inflammation, acute		3 (6%)	
Inflammation, chronic active	2 (4%)	1 (2%)	3 (6%)
Ulcer	6 (12%)	5 (10%)	9 (18%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(50)	(50)	(50)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic active			2 (4%)
Mucosa, dilatation	27 (54%)	26 (52%)	28 (56%)
Mucosa, erosion	6 (12%)	4 (8%)	5 (10%)
Mucosa, mineralization			1 (2%)
Mucosa, pigmentation	1 (2%)		
Mucosa, ulcer	2 (4%)		
Serosa, inflammation, chronic active			1 (2%)
Tooth		(1)	(2)
Peridontal tissue, inflammation, chronic			1 (50%)
Pulp, inflammation, chronic			1 (50%)
Pulp, inflammation, chronic active		1 (100%)	
CARDIOVASCULAR SYSTEM			
Blood vessel	(50)	(50)	(50)
Aorta, mineralization			1 (2%)
Heart	(50)	(50)	(50)
Cardiomyopathy, chronic	48 (96%)	50 (100%)	47 (94%)
Inflammation, acute	1 (2%)		
Mineralization	1 (2%)		1 (2%)
Artery, mineralization			1 (2%)
Atrium, thrombus	2 (4%)	1 (2%)	1 (2%)
Ventricle, thrombus	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(49)	(49)
Congestion			1 (2%)
Degeneration, fatty	33 (66%)	31 (63%)	37 (76%)
Hematopoietic cell proliferation		1 (2%)	
Hemorrhage		1 (2%)	
Hyperplasia	16 (32%)	19 (39%)	9 (18%)
Hypertrophy	4 (8%)	9 (18%)	4 (8%)
Inflammation, chronic			1 (2%)
Pigmentation	50 (100%)	48 (98%)	48 (98%)
Adrenal gland, medulla	(49)	(48)	(49)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia	4 (8%)	4 (8%)	6 (12%)
Islets, pancreatic	(50)	(49)	(50)
Hyperplasia	1 (2%)	1 (2%)	
Parathyroid gland	(42)	(44)	(41)
Hypertrophy			1 (2%)
Pituitary gland	(50)	(50)	(50)
Pars distalis, angiectasis	1 (2%)	3 (6%)	1 (2%)
Pars distalis, congestion			1 (2%)
Pars distalis, cyst	10 (20%)	14 (28%)	11 (22%)
Pars distalis, hemorrhage	3 (6%)		1 (2%)
Pars distalis, hyperplasia	7 (14%)	17 (34%)	7 (14%)
Pars distalis, metaplasia, osseous		1 (2%)	
Pars intermedia, angiectasis	1 (2%)	2 (4%)	2 (4%)
Pars intermedia, cyst	1 (2%)		
Pars nervosa, cyst		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)		
Ultimobranchial cyst		1 (2%)	2 (4%)
C-cell, hyperplasia	17 (34%)	23 (46%)	15 (30%)
Follicle, ectasia		4 (8%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE *(Continued)*

	Chamber Control	600 ppm	1,200 ppm
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(49)	(50)	(44)
Cyst	1 (2%)		
Hyperplasia		2 (4%)	2 (5%)
Inflammation, acute	1 (2%)		2 (5%)
Inflammation, chronic	21 (43%)	20 (40%)	21 (48%)
Inflammation, chronic active	10 (20%)	14 (28%)	7 (16%)
Duct, ectasia	2 (4%)		1 (2%)
Duct, hyperplasia, squamous			1 (2%)
Ovary	(50)	(50)	(50)
Follicle, cyst			1 (2%)
Periovarian tissue, cyst	2 (4%)	1 (2%)	2 (4%)
Uterus	(50)	(50)	(50)
Ectasia	2 (4%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)		
Prolapse	1 (2%)		
Endometrium, ectasia			1 (2%)
Endometrium, hyperplasia, cystic	2 (4%)	2 (4%)	7 (14%)
Endometrium, inflammation, chronic		1 (2%)	1 (2%)
Myometrium, inflammation, chronic			1 (2%)
Vagina	(4)	(4)	(3)
Inflammation, acute			1 (33%)
Inflammation, chronic active	1 (25%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(50)	(50)
Hyperplasia			1 (2%)
Myelofibrosis	8 (16%)	9 (18%)	4 (8%)
Myeloid cell, hyperplasia	1 (2%)		
Lymph node	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	6 (12%)	3 (6%)	10 (20%)
Inflammation, acute	1 (2%)		1 (2%)
Pigmentation		1 (2%)	
Mediastinal, congestion		1 (2%)	
Mediastinal, hemorrhage	1 (2%)		
Mediastinal, hyperplasia, lymphoid		1 (2%)	2 (4%)
Mediastinal, pigmentation			1 (2%)
Mesenteric, congestion	4 (8%)	3 (6%)	4 (8%)
Mesenteric, edema	1 (2%)		
Mesenteric, hyperplasia, lymphoid	17 (34%)	32 (64%)	29 (58%)
Mesenteric, inflammation, acute	1 (2%)	1 (2%)	
Renal, congestion		1 (2%)	
Lymph node, mandibular	(47)	(48)	(42)
Congestion	5 (11%)	8 (17%)	3 (7%)
Cyst	1 (2%)	1 (2%)	2 (5%)
Hyperplasia, lymphoid	41 (87%)	42 (88%)	39 (93%)
Inflammation, acute	1 (2%)		1 (2%)
Spleen	(50)	(50)	(50)
Fibrosis		3 (6%)	3 (6%)
Hematopoietic cell proliferation	41 (82%)	46 (92%)	44 (88%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, reticulum cell	1 (2%)		
Infarct		1 (2%)	1 (2%)
Pigmentation	44 (88%)	44 (88%)	47 (94%)
Capsule, fibrosis		2 (4%)	
Capsule, inflammation, acute			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Thymus	(46)	(46)	(46)
Congestion	4 (9%)	2 (4%)	1 (2%)
Cyst	2 (4%)	2 (4%)	3 (7%)
Hyperplasia, lymphoid		3 (7%)	1 (2%)
Mediastinum, inflammation, chronic active	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic active	1 (2%)		
Acinus, ectasia	37 (74%)	34 (68%)	27 (54%)
Acinus, hyperplasia	3 (6%)	1 (2%)	
Acinus, hyperplasia, cystic			1 (2%)
Duct, ectasia	21 (42%)	31 (62%)	23 (46%)
Skin	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)
Head, inflammation, chronic active	1 (2%)	1 (2%)	
Head, ulcer			1 (2%)
Lip, inflammation, chronic active		1 (2%)	
Subcutaneous tissue, abscess			1 (2%)
Subcutaneous tissue, head, abscess			1 (2%)
Subcutaneous tissue, head, granuloma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(50)	(50)
Cranium, fibrous osteodystrophy	1 (2%)		2 (4%)
Cranium, osteopetrosis	2 (4%)	1 (2%)	
Femur, fibrous osteodystrophy	1 (2%)		4 (8%)
Femur, osteopetrosis	3 (6%)	1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Compression	11 (22%)	6 (12%)	13 (27%)
Gliosis	1 (2%)		
Hemorrhage	5 (10%)	6 (12%)	3 (6%)
Hydrocephalus	1 (2%)	2 (4%)	
Lateral ventricle, hemorrhage	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	5 (10%)	5 (10%)	6 (12%)
Hemorrhage	7 (14%)	7 (14%)	4 (8%)
Infiltration cellular		1 (2%)	
Infiltration cellular, lymphocytic	49 (98%)	49 (98%)	50 (100%)
Metaplasia, osseous		1 (2%)	
Pigmentation, cholesterol	1 (2%)		2 (4%)
Alveolar epithelium, hyperplasia		1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocytic	28 (56%)	20 (40%)	36 (72%)
Alveolus, mineralization	1 (2%)		
Arteriole, mineralization	25 (50%)	30 (60%)	26 (52%)
Interstitium, inflammation, chronic	17 (34%)	9 (18%)	2 (4%)
Interstitium, inflammation, chronic active	1 (2%)	2 (4%)	4 (8%)
Peribronchiolar, inflammation, acute	2 (4%)	1 (2%)	
Peribronchiolar, inflammation, chronic		5 (10%)	1 (2%)
Peribronchiolar, inflammation, chronic active			1 (2%)
Pleura, fibrosis			1 (2%)
Smooth muscle, hyperplasia			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	600 ppm	1,200 ppm
RESPIRATORY SYSTEM (Continued)			
Nose	(49)	(50)	(50)
Glands, hyperplasia			1 (2%)
Lumen, foreign body	4 (8%)	1 (2%)	1 (2%)
Lumen, hemorrhage	30 (61%)	34 (68%)	32 (64%)
Mucosa, inflammation		1 (2%)	
Mucosa, inflammation, acute	27 (55%)	41 (82%)	41 (82%)
Nasolacrimal duct, hemorrhage	1 (2%)		
Nasolacrimal duct, inflammation, acute	5 (10%)	2 (4%)	6 (12%)
Nasolacrimal duct, inflammation, chronic active		1 (2%)	
Olfactory epithelium, degeneration	44 (90%)	48 (96%)	47 (94%)
Olfactory epithelium, erosion	2 (4%)	11 (22%)	10 (20%)
Olfactory epithelium, hemorrhage			1 (2%)
Olfactory epithelium, metaplasia		1 (2%)	5 (10%)
Olfactory epithelium, metaplasia, squamous		1 (2%)	1 (2%)
Respiratory epithelium, degeneration	29 (59%)	45 (90%)	39 (78%)
Respiratory epithelium, erosion	4 (8%)	1 (2%)	3 (6%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)	
Trachea	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic active		1 (2%)	
SPECIAL SENSES SYSTEM			
Eye	(5)	(4)	(3)
Atrophy	1 (20%)	1 (25%)	
Cataract	3 (60%)	2 (50%)	2 (67%)
Hemorrhage		1 (25%)	
Anterior chamber, hemorrhage			1 (33%)
Lids, inflammation, chronic active			1 (33%)
Retina, degeneration	4 (80%)	3 (75%)	2 (67%)
Sclera, mineralization	2 (40%)	2 (50%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Hydronephrosis			1 (2%)
Inflammation, acute	1 (2%)		
Nephropathy, chronic	49 (98%)	48 (96%)	49 (98%)
Capsule, inflammation, chronic			1 (2%)
Pelvis, calculus micro observation only	1 (2%)	1 (2%)	
Renal tubule, cyst	2 (4%)		1 (2%)
Renal tubule, hyperplasia	1 (2%)	1 (2%)	
Renal tubule, hypertrophy		1 (2%)	
Renal tubule, pigmentation	49 (98%)	50 (100%)	48 (96%)
Urinary bladder	(50)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	60	60	60	60
ALIMENTARY SYSTEM				
Gallbladder	(59)	(54)	(57)	(59)
Lymphoma malignant mixed		1 (2%)		
Lymphoma malignant undifferentiated cell type				1 (2%)
Intestine large, cecum	(60)	(60)	(60)	(59)
Lymphoma malignant mixed	3 (5%)			
Lymphoma malignant undifferentiated cell type				1 (2%)
Intestine large, colon	(60)	(60)	(60)	(59)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed			2 (3%)	
Intestine small, jejunum	(60)	(60)	(60)	(60)
Lymphoma malignant mixed	1 (2%)	1 (2%)		
Lymphoma malignant undifferentiated cell type				1 (2%)
Liver	(60)	(60)	(60)	(59)
Hemangioma			1 (2%)	
Hemangiosarcoma	2 (3%)			1 (2%)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Hepatocellular carcinoma	13 (22%)	8 (13%)	9 (15%)	8 (14%)
Hepatocellular adenoma	7 (12%)	10 (17%)	9 (15%)	10 (17%)
Hepatocellular adenoma, multiple				1 (2%)
Histiocytic sarcoma				1 (2%)
Ito cell tumor malignant				1 (2%)
Lymphoma malignant histiocytic		2 (3%)		
Lymphoma malignant mixed	2 (3%)	2 (3%)	2 (3%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Mesentery	*(60)	*(60)	*(60)	*(60)
Lymphoma malignant mixed	1 (2%)		1 (2%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Pancreas	(60)	(60)	(60)	(59)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed	2 (3%)		3 (5%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Salivary glands	(60)	(60)	(60)	(59)
Lymphoma malignant mixed	3 (5%)	2 (3%)	3 (5%)	
Stomach, forestomach	(60)	(59)	(60)	(60)
Lymphoma malignant mixed			1 (2%)	
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(60)	(60)	(60)	(60)
Lymphoma malignant mixed			1 (2%)	
Tooth	*(60)	*(60)	*(60)	*(60)
Pulp, lymphoma malignant undifferentiated cell type				1 (2%)
CARDIOVASCULAR SYSTEM				
Heart	(60)	(60)	(60)	(59)
Hemangiosarcoma				1 (2%)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant mixed			1 (2%)	
ENDOCRINE SYSTEM				
Adrenal gland	(60)	(60)	(59)	(60)
Lymphoma malignant mixed		1 (2%)		
Capsule, spindle cell, adenoma	1 (2%)			
Adrenal gland, cortex	(60)	(60)	(59)	(59)
Adenoma			1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ENDOCRINE SYSTEM (Continued)				
Islets, pancreatic	(60)	(60)	(60)	(58)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(59)	(58)	(58)	(56)
Pars distalis, adenoma		2 (3%)	1 (2%)	
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(60)	(60)	(60)	(59)
Follicle, adenoma	1 (2%)	2 (3%)		
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(60)	(60)	(60)	(60)
Lymphoma malignant histiocytic		2 (3%)		
Lymphoma malignant mixed			1 (2%)	
Preputial gland	*(60)	*(60)	*(60)	*(60)
Lymphoma malignant mixed			1 (2%)	
Prostate	(60)	(60)	(59)	(59)
Lymphoma malignant mixed	1 (2%)		1 (2%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Seminal vesicle	*(60)	*(60)	*(60)	*(60)
Lymphoma malignant mixed	1 (2%)			
Testes	(60)	(60)	(60)	(60)
Lymphoma malignant mixed	1 (2%)		1 (2%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Interstitial cell, adenoma		1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(60)	(60)	(59)
Hemangiosarcoma, metastatic, liver	1 (2%)			
Hemangiosarcoma, metastatic, spleen				1 (2%)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant mixed	1 (2%)	1 (2%)		
Lymph node	(60)	(60)	(59)	(59)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Axillary, lymphoma malignant mixed	1 (2%)	1 (2%)		
Iliac, lymphoma malignant mixed	2 (3%)	2 (3%)	1 (2%)	
Iliac, lymphoma malignant undifferentiated cell type				1 (2%)
Mediastinal, histiocytic sarcoma				1 (2%)
Mediastinal, lymphoma malignant mixed	1 (2%)	2 (3%)	2 (3%)	
Mediastinal, lymphoma malignant undifferentiated cell type				1 (2%)
Mesenteric, hemangiosarcoma, metastatic, liver	1 (2%)			
Mesenteric, histiocytic sarcoma				1 (2%)
Mesenteric, lymphoma malignant histiocytic		2 (3%)		
Mesenteric, lymphoma malignant lymphocytic			1 (2%)	
Mesenteric, lymphoma malignant mixed	5 (8%)	6 (10%)	6 (10%)	3 (5%)
Mesenteric, lymphoma malignant undifferentiated cell type				1 (2%)
Renal, histiocytic sarcoma				1 (2%)
Renal, lymphoma malignant mixed	2 (3%)	1 (2%)	1 (2%)	
Renal, lymphoma malignant undifferentiated cell type				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node, mandibular	(53)	(52)	(54)	(51)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed	3 (6%)	2 (4%)	4 (7%)	2 (4%)
Lymphoma malignant undifferentiated cell type				1 (2%)
Spleen	(60)	(60)	(60)	(59)
Hemangiosarcoma			1 (2%)	3 (5%)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant histiocytic		3 (5%)		
Lymphoma malignant mixed	5 (8%)	5 (8%)	6 (10%)	3 (5%)
Lymphoma malignant undifferentiated cell type				1 (2%)
Thymus	(53)	(59)	(58)	(54)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant mixed	2 (4%)	2 (3%)	3 (5%)	1 (2%)
Lymphoma malignant undifferentiated cell type				1 (2%)
INTEGUMENTARY SYSTEM				
Skin	(60)	(60)	(60)	(58)
Lymphoma malignant mixed			1 (2%)	
Neck, subcutaneous tissue, hemangioma		1 (2%)		
MUSCULOSKELETAL SYSTEM				
Bone	(60)	(60)	(60)	(60)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Skeletal muscle	*(60)	*(60)	*(60)	*(60)
Head, lymphoma malignant mixed			1 (2%)	
NERVOUS SYSTEM				
Brain	(60)	(60)	(60)	(60)
Lymphoma malignant mixed		1 (2%)	1 (2%)	
RESPIRATORY SYSTEM				
Lung	(60)	(60)	(60)	(60)
Adenocarcinoma, metastatic, harderian gland			1 (2%)	
Alveolar/bronchiolar adenoma	8 (13%)	1 (2%)	2 (3%)	7 (12%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma	2 (3%)	1 (2%)		1 (2%)
Hepatocellular carcinoma, metastatic, liver	3 (5%)		1 (2%)	1 (2%)
Histiocytic sarcoma				1 (2%)
Lymphoma malignant histiocytic		2 (3%)		
Lymphoma malignant mixed	3 (5%)	3 (5%)	2 (3%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
Nose	(59)	(59)	(60)	(59)
Adenocarcinoma, metastatic, harderian gland			1 (2%)	
Mucosa, lymphoma malignant mixed			1 (2%)	
Submucosa, lymphoma malignant undifferentiated cell type				1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland	*(60)	*(60)	*(60)	*(60)
Adenocarcinoma			1 (2%)	
Adenoma		3 (5%)		2 (3%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
URINARY SYSTEM				
Kidney	(60)	(60)	(60)	(59)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Lipoma		1 (2%)		
Lymphoma malignant mixed	4 (7%)	4 (7%)	3 (5%)	1 (2%)
Urinary bladder	(60)	(60)	(60)	(59)
Lymphoma malignant mixed	2 (3%)	2 (3%)	3 (5%)	
Lymphoma malignant undifferentiated cell type				1 (2%)
SYSTEMIC LESIONS				
Multiple organs	*(60)	*(60)	*(60)	*(60)
Lymphoma malignant mixed	5 (8%)	7 (12%)	6 (10%)	3 (5%)
Hemangiosarcoma	2 (3%)		1 (2%)	5 (8%)
Lymphoma malignant histiocytic		3 (5%)		
Hemangioma		1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic			2 (3%)	
Lymphoma malignant undifferentiated cell				1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	60	60	60	60
Moribund	19	19	25	17
Terminal sacrifice	17	21	16	19
Dead	23	19	14	21
Accident	1		2	2
Natural death		1	3	1
TUMOR SUMMARY				
Total animals with primary neoplasms **	29	29	26	33
Total primary neoplasms	42	41	35	50
Total animals with benign neoplasms	16	18	14	19
Total benign neoplasms	18	22	16	24
Total animals with malignant neoplasms	20	16	17	17
Total malignant neoplasms	24	19	19	26
Total animals with secondary neoplasms ***	4		3	2
Total secondary neoplasms	5		5	4

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: CHAMBER CONTROL

WEEKS ON STUDY	042	042	042	048	054	056	062	062	063	063	064	064	064	064	068	071	075	076	076	077	078	079	079	080	081
CARCASS ID	061	481	591	461	331	521	191	101	321	091	281	041	431	011	261	401	371	411	581	221	241	111	231	071	541
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Hepatocellular carcinoma									X									X				X	X		
Hepatocellular adenoma														X		X				X					
Lymphoma malignant mixed																									
Mesentery																									
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+												
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, spindle cell, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	+	+	M	+	M	M	+	+	+	+	M	+	M	+	+	M	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis						+							+		+	+		+	+	+		+	+		
Preputial gland			+	+				+	M				+	+		+	+			+					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Seminal vesicle									+									+							
Lymphoma malignant mixed																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

+: Tissue examined microscopically
 : Not examined
−: Present but not examined microscopically
I: Insufficient tissue

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

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

WEEKS ON STUDY	083	083	085	087	087	088	089	090	090	091	091	092	092	096	101	102	102	102	105	105	105	105	105	105	105
CARCASS ID	201	531	551	391	131	361	381	511	561	151	271	451	291	081	181	601	501	571	021	121	141	251	491	301	441
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X						X				X
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Hepatocellular carcinoma					X							X	X			X	X						X		
Hepatocellular adenoma										X		X													X
Lymphoma malignant mixed															X										
Mesentery															+								+		
Lymphoma malignant mixed															X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				X
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, spindle cell, adenoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	+	M	+	+	M	M	M	+	M	M	+	M	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis		+		+	+			+	+		+			+											
Preputial gland						+	+					+	+												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Seminal vesicle																									+
Lymphoma malignant mixed																									X
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									X

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	031	051	211	341	171	421	161	311	351	471	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	59
Gallbladder	+	+	+	+	+	+	+	+	+	+	59
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											3
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											2
Hepatocellular carcinoma		X			X			X			13
Hepatocellular adenoma							X				7
Lymphoma malignant mixed		X									2
Mesentery											2
Lymphoma malignant mixed											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed		X									2
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed		X									3
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Papilloma squamous									X		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tooth				+							2
CARDIOVASCULAR SYSTEM											
Blood vessel	+	+	+	+	+	+	+	+	+	+	59
Heart	+	+	+	+	+	+	+	+	+	+	60
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Capsule, spindle cell, adenoma							X				1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	M	M	M	M	M	+	M	M	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicle, adenoma								X			1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis						+					17
Preputial gland											12
Prostate	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1
Seminal vesicle							+				4
Lymphoma malignant mixed											1
Testes	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1

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

WEEKS ON STUDY	042	042	042	048	054	056	062	062	063	063	064	064	064	064	068	071	075	076	076	077	078	079	079	080	081
CARCASS ID	061	481	591	461	331	521	191	101	321	091	281	041	431	011	261	401	371	411	581	221	241	111	231	071	541
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																									
Lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Axillary, lymphoma malignant mixed																									
Iliac, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, hemangiosarcoma, metastatic, liver																									
Mesenteric, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																		X							
Lymphoma malignant mixed																									
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Ureter				+			+							+				+	+	+			+		
Urethra	+	+																+				+			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

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

WEEKS ON STUDY	083	083	085	087	087	088	089	090	090	091	091	092	092	096	101	102	102	102	105	105	105	105	105	105	105
CARCASS ID	201	531	551	391	131	361	381	511	561	151	271	451	291	081	181	601	501	571	021	121	141	251	491	301	441
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver																								X	
Lymphoma malignant mixed																									X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Axillary, lymphoma malignant mixed															X										
Iliac, lymphoma malignant mixed															X										X
Mediastinal, lymphoma malignant mixed															X										
Mesenteric, hemangiosarcoma, metastatic, liver																								X	
Mesenteric, lymphoma malignant mixed															X						X				X
Renal, lymphoma malignant mixed															X										X
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant mixed															X						X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X						X				X
Thymus	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed																									X
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X	X					X	X		X					X					
Alveolar/bronchiolar carcinoma							X										X								
Hepatocellular carcinoma, metastatic, liver																				X					
Lymphoma malignant mixed															X										X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X						X				X
Ureter							+																		
Urethra				+																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										X

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

WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	0 3 1	0 5 1	2 1 1	3 4 1	1 7 1	4 2 1	1 6 1	3 1 1	3 5 1	4 7 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma, metastatic, liver											1
Lymphoma malignant mixed											1
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Histiocytic sarcoma											1
Axillary, lymphoma malignant mixed											1
Iliac, lymphoma malignant mixed											2
Mediastinal, lymphoma mal. mixed											1
Mesenteric, hemangiosarcoma, metastatic, liver											1
Mesenteric, lymphoma malignant mixed		X	X								5
Renal, lymphoma malignant mixed											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	53
Lymphoma malignant mixed		X									3
Spleen	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed		X	X								5
Thymus	+	+	+	+	+	M	+	+	M	+	53
Histiocytic sarcoma											1
Lymphoma malignant mixed		X									2
INTEGUMENTARY SYSTEM											
Mammary gland	+	M	M	M	+	M	M	M	M	M	6
Skin	+	+	+	+	+	+	+	+	+	+	60
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma	X		X								8
Alveolar/bronchiolar carcinoma											2
Hepatocellular carcinoma, metastatic, liver		X									3
Lymphoma malignant mixed		X									3
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
None											
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed		X									4
Ureter											8
Urethra											5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 120 ppm

WEEKS ON STUDY	023	056	057	058	060	063	064	065	072	072	072	073	075	076	076	080	080	081	081	082	083	084	085	085	087
CARCASS ID	4141	4191	3821	4181	4131	4121	3911	3811	4171	3761	3851	3731	3971	3951	4051	3661	3931	3621	3711	3841	3941	3651	3751	4071	3901
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	M	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X										X	
Hepatocellular adenoma											X		X			X									
Lymphoma malignant histiocytic																	X								
Lymphoma malignant mixed																								X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																+									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Lymphoma malignant mixed																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	-	+	M	+	+	+	M	M	M	M	M	M	+	+	+	M	M	M	M	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Penis														+							+		+	+	+
Preputial gland	+		+				+							+											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle					+									+											+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Interstitial cell, adenoma																X									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	088	088	089	091	091	091	092	092	092	095	099	103	104	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	4091	4151	3681	3721	3741	4201	3891	4111	3691	3831	3781	4001	4021	3671	3801	3991	4031	4061	3791	3871	3881	3961	4161	3631	4041
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant mixed																X									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X							X					X	X						X				
Hepatocellular adenoma										X		X							X		X		X		
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																					X				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth														+		+			+					+	
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	+	+	+	M	+	+	M	M	+	M	M	M	M	+	M	+	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenoma		X																							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Penis	+		+	+	+			+		+	+	+	+		+				+			+			
Preputial gland										+	+			+											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle							+																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	4101	3611	3641	3701	3861	4081	3771	3921	3981	4011	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	+	+	+	+	+	+	54
Lymphoma malignant mixed											1
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma				X							8
Hepatocellular adenoma	X						X				10
Lymphoma malignant histiocytic									X		2
Lymphoma malignant mixed											2
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed					X						2
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tooth		+		+				+			8
CARDIOVASCULAR SYSTEM											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant histiocytic				X							1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	M	M	+	+	M	M	+	M	M	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	58
Pars distalis, adenoma						X					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Follicle, adenoma										X	2
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant histiocytic				X					X		2
Penis		+					+	+		+	21
Preputial gland			+							+	9
Prostate	+	+	+	+	+	+	+	+	+	+	60
Seminal vesicle											4
Testes	+	+	+	+	+	+	+	+	+	+	60
Interstitial cell, adenoma											1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	0 2 3	0 5 6	0 5 7	0 5 8	0 6 0	0 6 3	0 6 4	0 6 5	0 7 2	0 7 2	0 7 2	0 7 3	0 7 5	0 7 6	0 7 6	0 8 0	0 8 0	0 8 1	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 8 5	0 8 7
CARCASS ID	4 1 4 1	4 1 9 1	3 8 2 1	4 1 8 1	4 1 3 1	4 1 2 1	3 9 1 1	3 8 1 1	4 1 7 1	3 7 6 1	3 8 5 1	3 7 3 1	3 9 7 1	3 9 5 1	4 0 5 1	3 6 6 1	3 9 3 1	3 6 2 1	3 7 1 1	3 8 4 1	3 9 4 1	3 6 5 1	3 7 5 1	4 0 7 1	3 9 0 1
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant mixed																									
Iliac, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant histiocytic																	X								
Mesenteric, lymphoma malignant mixed																								X	
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	M	M	+	M	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																	X								
Lymphoma malignant mixed																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neck, subcutaneous tissue, hemangioma																									X
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																			+						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Lymphoma malignant histiocytic																								X	
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland				+																					
Adenoma				X																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Lymphoma malignant mixed																									
Ureter																									
Urethra	+			+	+									+											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	088	088	089	091	091	091	092	092	092	095	099	103	104	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	4091	4151	3681	3721	3741	4201	3891	4111	3691	3831	3781	4001	4021	3671	3801	3991	4031	4061	3791	3871	3881	3961	4161	3631	4041
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																X									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant mixed																X									
Iliac, lymphoma malignant mixed																X			X						
Mediastinal, lymphoma malignant mixed																X							X		
Mesenteric, lymphoma malignant histiocytic																									
Mesenteric, lymphoma malignant mixed													X			X			X				X		
Renal, lymphoma malignant mixed																X									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																X							X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed													X			X			X				X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																X							X		
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neck, subcutaneous tissue, hemangioma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X		
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																							X		
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																X							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland						+	+																		
Adenoma						X	X																		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma										X															
Lymphoma malignant mixed										X						X							X		
Ureter											+														
Urethra								+					+												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																X							X		

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	4101	3611	3641	3701	3861	4081	3771	3921	3981	4011	
HEMATOPOIETIC SYSTEM											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant histiocytic				X							1
Lymphoma malignant mixed											1
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Axillary, lymphoma malignant mixed											1
Iliac, lymphoma malignant mixed											2
Mediastinal, lymphoma mal mixed											2
Mesenteric, lymphoma malignant histiocytic				X							2
Mesenteric, lymphoma malignant mixed					X						6
Renal, lymphoma malignant mixed											1
Lymph node mandibular	+	+	+	+	+	+	+	+	+	+	52
Lymphoma malignant histiocytic				X							1
Lymphoma malignant mixed											2
Spleen	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant histiocytic				X					X		3
Lymphoma malignant mixed					X						5
Thymus	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant histiocytic				X							1
Lymphoma malignant mixed											2
INTEGUMENTARY SYSTEM											
Mammary gland	M	M	M	M	M	M	M	+	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	60
Neck, subcutaneous tissue, hemangioma											1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle								+			2
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											1
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Alveolar/bronchiolar carcinoma											1
Lymphoma malignant histiocytic				X					X		2
Lymphoma malignant mixed											3
Nose	+	+	+	+	M	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Harderian gland											3
Adenoma											3
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Lipoma											1
Lymphoma malignant mixed					X						4
Ureter											1
Urethra											6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed											2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 600 ppm

WEEKS ON STUDY	033	040	040	044	046	047	048	054	055	056	058	060	061	062	062	064	064	065	065	068	068	070	072	073	074
CARCASS ID	1251	1361	1321	1801	1571	1441	1381	1261	1231	1631	1391	1411	1351	1541	1581	1551	1651	1531	1401	1741	1371	1291	1421	1221	1751
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hepatocellular carcinoma													X				X								
Hepatocellular adenoma					X			X										X							
Lymphoma malignant mixed																									
Mesentery																									
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Tooth																								+	
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	M	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Penis							+			+			+			+			+		+				
Preputial gland							+	+		+						+	+					+			
Lymphoma malignant mixed																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Seminal vesicle					+			+																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	079	080	080	081	081	081	082	083	083	089	091	092	092	092	097	099	103	104	104	105	105	105	105	105	105
CARCASS ID	1511	1661	1621	1301	1591	1731	1791	1431	1311	1281	1451	1341	1691	1711	1271	1241	1481	1471	1721	1501	1671	1761	1781	1331	1681
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																								X	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma												X													
Hepatocellular carcinoma	X				X										X	X		X				X			
Hepatocellular adenoma							X		X																
Lymphoma malignant mixed												X													
Mesentery					+																				
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed												X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Papilloma squamous																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Tooth											+														
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	M	M	M	M	M	M	+	+	+	+	+	+	M	M	M	M	+	M	M	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Penis	+		+		+		+		+	+	+		+		+		+								
Preputial gland																	+	+	+						
Lymphoma malignant mixed																									
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Seminal vesicle	+					+																			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	1771	1491	1561	1601	1611	1521	1641	1211	1461	1701	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Gallbladder	+	+	+	+	M	+	+	+	+	+	57
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed									X		2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	60
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Liver	+	+	+	+	+	+	+	+	+	+	60
Hemangioma											1
Hepatocellular carcinoma		X									9
Hepatocellular adenoma					X	X		X		X	9
Lymphoma malignant mixed									X		2
Mesentery							+				2
Lymphoma malignant mixed							X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant lymphocytic											1
Lymphoma malignant mixed	X								X		3
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed							X		X		3
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
Tooth											2
CARDIOVASCULAR SYSTEM											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma						X					1
Parathyroid gland	M	M	M	M	M	M	M	M	M	M	25
Pituitary gland	+	+	+	+	+	+	M	+	+	+	58
Pars distalis, adenoma				X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
Penis								+			17
Preputial gland									+		10
Lymphoma malignant mixed									X		1
Prostate	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant mixed									X		1
Seminal vesicle											4
Testes	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	033	040	040	044	046	047	048	054	055	056	058	060	061	062	062	064	064	065	065	068	068	070	072	073	074
CARCASS ID	1251	1361	1321	1801	1571	1441	1381	1261	1231	1631	1391	1411	1351	1541	1581	1551	1651	1531	1401	1741	1371	1291	1421	1221	1751
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Hepatocellular carcinoma, metastatic, liver																									
Iliac, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant lymphocytic					X																				
Mesenteric, lymphoma malignant mixed																									
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Hemangiosarcoma																									
Lymphoma malignant mixed																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+							+			+													
Head, lymphoma malignant mixed																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Alveolar/bronchiolar adenoma																		X							
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland																									
Mucosa, lymphoma malignant mixed																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenocarcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Lymphoma malignant mixed																									
Ureter							+																		+
Urethra		+																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	079	080	080	081	081	081	082	083	083	089	091	092	092	092	097	099	103	104	104	105	105	105	105	105	105
CARCASS ID	1511	1661	1621	1301	1591	1731	1791	1431	1311	1281	1451	1341	1691	1711	1271	1241	1481	1471	1721	1501	1671	1761	1781	1331	1681
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																						X			
Iliac, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant mixed												X													
Mesenteric, lymphoma malignant lymphocytic																									
Mesenteric, lymphoma malignant mixed												X												X	
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Lymphoma malignant mixed												X												X	
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed												X												X	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+						+														
Head, lymphoma malignant mixed																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland												X													
Alveolar/bronchiolar adenoma																									X
Hepatocellular carcinoma, metastatic, liver																		X							
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, harderian gland												X													
Mucosa, lymphoma malignant mixed																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland												+													
Adenocarcinoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																						X			
Lymphoma malignant mixed												X													
Ureter	+																								
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																								X	

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	1771	1491	1561	1601	1611	1521	1641	1211	1461	1701	
HEMATOPOIETIC SYSTEM											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Hepatocellular carcinoma, metastatic, liver											1
Iliac, lymphoma malignant mixed							X				1
Mediastinal, lymphoma mal. mixed							X				2
Mesenteric, lymphoma malignant lymphocytic											1
Mesenteric, lymphoma malignant mixed	X						X	X	X		6
Renal, lymphoma malignant mixed							X				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	54
Lymphoma malignant lymphocytic					X						1
Lymphoma malignant mixed							X	X	X		4
Spleen	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma											1
Lymphoma malignant mixed	X						X	X	X		6
Thymus	+	+	+	+	+	+	+	M	+	+	58
Lymphoma malignant mixed									X		3
INTEGUMENTARY SYSTEM											
Mammary gland	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle									+		6
Head, lymphoma malignant mixed									X		1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed									X		1
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, harderian gland											1
Alveolar/bronchiolar adenoma											2
Hepatocellular carcinoma, metastatic, liver											1
Lymphoma malignant mixed							X		X		2
Nose	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, harderian gland											1
Mucosa, lymphoma malignant mixed									X		1
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Harderian gland											1
Adenocarcinoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma, metastatic, liver											1
Lymphoma malignant mixed							X		X		3
Ureter											3
Urethra											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant mixed							X		X		3

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 1,200 ppm

WEEKS ON STUDY	005	023	042	043	048	052	052	053	061	061	062	064	066	067	067	073	075	075	076	076	079	079	081	081	082
CARCASS ID	2631	2691	2411	2581	2461	2421	2441	2521	2541	2561	2791	2591	2571	2931	2801	2771	2761	2991	2881	2971	2611	2951	2811	2821	2601
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, spleen																									
Hepatocellular carcinoma								X					X												
Hepatocellular adenoma				X														X					X		X
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																									
Ito cell tumor malignant																									
Lymphoma malignant undifferentiated cell type																									
Mesentery																									
Lymphoma malignant undifferentiated cell type																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Pulp, lymphoma malignant undifferentiated cell type																									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Hemangiosarcoma																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	M	+	+	M	+	M	M	M	+	+	+	M	+	M	M	+	M	M	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis				+								+		+			+	+			+				+
Preputial gland	+	+										+		+	+										+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymphoma malignant undifferentiated cell type																									
Seminal vesicle								+			+										+	+			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Interstitial cell, adenoma																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	0 8 2	0 8 2	0 8 4	0 9 1	0 9 2	0 9 2	0 9 2	0 9 5	0 9 8	0 9 9	1 0 0	1 0 1	1 0 1	1 0 3	1 0 3	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	2 8 4 1	2 8 7 1	2 5 0 1	2 9 0 1	2 9 6 1	2 6 5 1	2 7 2 1	2 4 8 1	2 7 1 1	2 4 7 1	2 9 4 1	2 5 1 1	2 4 3 1	2 8 3 1	2 7 8 1	2 7 3 1	2 5 5 1	2 6 4 1	2 7 4 1	2 8 5 1	2 9 1 1	2 4 5 1	2 4 9 1	2 6 7 1	2 7 0 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Hemangiosarcoma, metastatic, spleen																									
Hepatocellular carcinoma			X								X		X		X							X			X
Hepatocellular adenoma		X				X						X		X											
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma										X															
Ito cell tumor malignant																			X						
Lymphoma malignant undifferentiated cell type																					X				
Mesentery																					+				
Lymphoma malignant undifferentiated cell type																					X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																					+				
Pulp, lymphoma malignant undifferentiated cell type																					X				
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Parathyroid gland	+	+	M	M	+	M	+	M	M	M	M	M	+	+	M	+	M	M	M	M	M	M	M	+	M
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars intermedia, adenoma																	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	+	+	+		+	+		+	+		+		+	+	+	+									
Preputial gland			+		+			+	+																+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Seminal vesicle										+			+												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				
Interstitial cell, adenoma																								X	

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	2751	2531	2891	2621	2661	2681	2921	2861	2981	3001	TOTAL TISSUES TUMORS
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	57
Gallbladder	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant undifferentiated cell type											1
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant undifferentiated cell type											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant undifferentiated cell type											1
Liver	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Hemangiosarcoma, metastatic, spleen				X							1
Hepatocellular carcinoma											8
Hepatocellular adenoma	X	X									10
Hepatocellular adenoma, multiple			X								1
Histiocytic sarcoma											1
Ito cell tumor malignant											1
Lymphoma malignant undifferentiated cell type											1
Mesentery											1
Lymphoma malignant undifferentiated cell type											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant undifferentiated cell type											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Tooth											1
Pulp, lymphoma malignant undifferentiated cell type											1
CARDIOVASCULAR SYSTEM											
Blood vessel	+	+	+	+	+	+	+	+	+	+	60
Heart	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma								X			1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	58
Adenoma											1
Parathyroid gland	M	+	M	+	M	M	M	M	+	+	24
Pituitary gland	+	+	+	+	+	+	+	+	+	+	56
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Penis	+								+		21
Preputial gland											11
Prostate	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant undifferentiated cell type											1
Seminal vesicle											6
Testes	+	+	+	+	+	+	+	+	+	+	60
Lymphoma malignant undifferentiated cell type											1
Interstitial cell, adenoma											1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	005	023	042	043	048	052	052	053	061	061	062	064	066	067	067	073	075	075	076	076	079	079	081	081	082
CARCASS ID	2631	2691	2411	2581	2461	2421	2441	2521	2541	2561	2791	2591	2571	2931	2801	2771	2761	2991	2881	2971	2611	2951	2811	2821	2601
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Lymph node	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, lymphoma malignant undifferentiated cell type																									
Mediastinal, histiocytic sarcoma																									
Mediastinal, lymphoma malignant undifferentiated cell type																									
Mesenteric, histiocytic sarcoma																									
Mesenteric, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant undifferentiated cell type																									
Renal, histiocytic sarcoma																									
Renal, lymphoma malignant undifferentiated cell type																									
Lymph node, mandibular	M	+	+	M	+	M	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	A	+	+	+	+	M
Histiocytic sarcoma																									
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Skeletal muscle																			+			+			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X															X		X
Alveolar/bronchiolar adenoma, multiple														X											
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Lymphoma malignant undifferentiated cell type																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Submucosa, lymphoma malignant undifferentiated cell type																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymphoma malignant mixed																									
Urethra				+												+									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	082	082	084	091	092	092	092	095	098	099	100	101	101	103	103	103	105	105	105	105	105	105	105	105	105
CARCASS ID	2841	2871	2501	2901	2961	2651	2721	2481	2711	2471	2941	2511	2431	2831	2781	2731	2551	2641	2741	2851	2911	2451	2491	2671	2701
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, lymphoma malignant undifferentiated cell type																					X				
Mediastinal, histiocytic sarcoma										X															
Mediastinal, lymphoma malignant undifferentiated cell type																					X				
Mesenteric, histiocytic sarcoma										X															
Mesenteric, lymphoma malignant mixed																						X			X
Mesenteric, lymphoma malignant undifferentiated cell type																					X				
Renal, histiocytic sarcoma										X															
Renal, lymphoma malignant undifferentiated cell type																					X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									X
Lymphoma malignant undifferentiated cell type																					X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma										X															
Lymphoma malignant mixed																						X			X
Lymphoma malignant undifferentiated cell type																					X				
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant mixed																									X
Lymphoma malignant undifferentiated cell type																					X				
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Skeletal muscle											+														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X									X			X					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma			X																						
Hepatocellular carcinoma, metastatic, liver											X														
Histiocytic sarcoma										X															
Lymphoma malignant undifferentiated cell type																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, lymphoma malignant undifferentiated cell type																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland				+							+													+	
Adenoma				X																				X	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									X
Urethra	+																								
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																					X				

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	2751	2531	2891	2621	2661	2681	2921	2861	2981	3001	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma, metastatic, spleen				X							1
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Iliac, lymphoma malignant undifferentiated cell type											1
Mediastinal, histiocytic sarcoma											1
Mediastinal, lymphoma malignant undifferentiated cell type											1
Mesenteric, histiocytic sarcoma											1
Mesenteric, lymphoma malignant mixed	X										3
Mesenteric, lymphoma malignant undifferentiated cell type											1
Renal, histiocytic sarcoma											1
Renal, lymphoma malignant undifferentiated cell type											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	51
Lymphoma malignant mixed	X										2
Lymphoma malignant undifferentiated cell type											1
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma			X	X			X				3
Histiocytic sarcoma											1
Lymphoma malignant mixed	X										3
Lymphoma malignant undifferentiated cell type											1
Thymus	+	+	+	+	+	+	+	+	+	+	54
Histiocytic sarcoma											1
Lymphoma malignant mixed											1
Lymphoma malignant undifferentiated cell type											1
INTEGUMENTARY SYSTEM											
Mammary gland	M	M	M	+	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	58
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Hemangiosarcoma, metastatic, spleen				X							1
Skeletal muscle											3
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma									X		7
Alveolar/bronchiolar adenoma, multiple											1
Alveolar/bronchiolar carcinoma											1
Hepatocellular carcinoma, metastatic, liver											1
Histiocytic sarcoma											1
Lymphoma malignant undifferentiated cell type											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Submucosa, lymphoma malignant undifferentiated cell type											1
Trachea	+	+	+	+	+	+	+	+	+	+	59
SPECIAL SENSES SYSTEM											
Harderian gland											3
Adenoma											2
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant mixed											1
Urethra											3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Lymphoma malignant undifferentiated cell type											1

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Harderian Gland: Adenoma				
Overall Rates (a)	0/60 (0%)	3/60 (5%)	0/60 (0%)	2/60 (3%)
Adjusted Rates (b)	0.0%	8.1%	0.0%	8.2%
Terminal Rates (c)	0/17 (0%)	0/22 (0%)	0/16 (0%)	1/19 (5%)
Day of First Observation		400		633
Life Table Tests (d)	P=0.491	P=0.152	(e)	P=0.275
Logistic Regression Tests (d)	P=0.472	P=0.107	(e)	P=0.253
Cochran-Armitage Trend Test (d)	P=0.477			
Fisher Exact Test (d)		P=0.122	(e)	P=0.248
Harderian Gland: Adenoma or Adenocarcinoma				
Overall Rates (a)	0/60 (0%)	3/60 (5%)	1/60 (2%)	2/60 (3%)
Adjusted Rates (b)	0.0%	8.1%	4.2%	8.2%
Terminal Rates (c)	0/17 (0%)	0/22 (0%)	0/16 (0%)	1/19 (5%)
Day of First Observation		400	639	633
Life Table Tests (d)	P=0.459	P=0.152	P=0.500	P=0.275
Logistic Regression Tests (d)	P=0.431	P=0.107	P=0.485	P=0.253
Cochran-Armitage Trend Test (d)	P=0.437			
Fisher Exact Test (d)		P=0.122	P=0.500	P=0.248
Liver: Hepatocellular Adenoma				
Overall Rates (f)	7/60 (12%)	10/60 (17%)	9/60 (15%)	11/59 (19%)
Adjusted Rates (b)	24.1%	33.2%	34.4%	34.3%
Terminal Rates (c)	2/17 (12%)	5/22 (23%)	4/16 (25%)	3/19 (16%)
Day of First Observation	446	501	319	297
Life Table Tests (d)	P=0.246	P=0.475	P=0.332	P=0.305
Logistic Regression Tests (d)	P=0.226	P=0.347	P=0.377	P=0.212
Cochran-Armitage Trend Test (d)	P=0.241			
Fisher Exact Test (d)		P=0.301	P=0.395	P=0.210
Liver: Hepatocellular Carcinoma				
Overall Rates (f)	13/60 (22%)	8/60 (13%)	9/60 (15%)	8/59 (14%)
Adjusted Rates (b)	44.5%	27.1%	32.7%	27.1%
Terminal Rates (c)	4/17 (24%)	4/22 (18%)	2/16 (13%)	2/19 (11%)
Day of First Observation	436	526	425	366
Life Table Tests (d)	P=0.263N	P=0.088N	P=0.315N	P=0.138N
Logistic Regression Tests (d)	P=0.261N	P=0.119N	P=0.293N	P=0.165N
Cochran-Armitage Trend Test (d)	P=0.242N			
Fisher Exact Test (d)		P=0.168N	P=0.240N	P=0.179N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (f)	19/60 (32%)	17/60 (28%)	18/60 (30%)	19/59 (32%)
Adjusted Rates (b)	57.9%	51.0%	57.9%	53.2%
Terminal Rates (c)	6/17 (35%)	8/22 (36%)	6/16 (38%)	5/19 (26%)
Day of First Observation	436	501	319	297
Life Table Tests (d)	P=0.432	P=0.210N	P=0.537	P=0.457N
Logistic Regression Tests (d)	P=0.400	P=0.326N	P=0.573N	P=0.566
Cochran-Armitage Trend Test (d)	P=0.438			
Fisher Exact Test (d)		P=0.421N	P=0.500N	P=0.553
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (f)	8/60 (13%)	1/60 (2%)	2/60 (3%)	8/60 (13%)
Adjusted Rates (b)	32.9%	4.5%	8.4%	26.2%
Terminal Rates (c)	3/17 (18%)	1/22 (5%)	1/16 (6%)	3/19 (16%)
Day of First Observation	613	729	450	366
Life Table Tests (d)	P=0.228	P=0.010N	P=0.068N	P=0.516N
Logistic Regression Tests (d)	P=0.210	P=0.010N	P=0.062N	P=0.591N
Cochran-Armitage Trend Test (d)	P=0.224			
Fisher Exact Test (d)		P=0.016N	P=0.047N	P=0.605N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (f)	9/60 (15%)	1/60 (2%)	2/60 (3%)	9/60 (15%)
Adjusted Rates (b)	36.4%	4.5%	8.4%	28.4%
Terminal Rates (c)	3/17 (18%)	1/22 (5%)	1/16 (6%)	3/19 (16%)
Day of First Observation	613	729	450	366
Life Table Tests (d)	P=0.205	P=0.005N	P=0.042N	P=0.508N
Logistic Regression Tests (d)	P=0.187	P=0.005N	P=0.037N	P=0.584N
Cochran-Armitage Trend Test (d)	P=0.200			
Fisher Exact Test (d)		P=0.008N	P=0.027N	P=0.601N
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	2/60 (3%)	0/60 (0%)	1/60 (2%)	5/60 (8%)
Adjusted Rates (b)	8.2%	0.0%	6.3%	23.6%
Terminal Rates (c)	1/17 (6%)	0/22 (0%)	1/16 (6%)	4/19 (21%)
Day of First Observation	543		729	638
Life Table Tests (d)	P=0.030	P=0.199N	P=0.530N	P=0.264
Logistic Regression Tests (d)	P=0.032	P=0.223N	P=0.531N	P=0.250
Cochran-Armitage Trend Test (d)	P=0.031			
Fisher Exact Test (d)		P=0.248N	P=0.500N	P=0.219
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (a)	2/60 (3%)	1/60 (2%)	2/60 (3%)	5/60 (8%)
Adjusted Rates (b)	8.2%	2.8%	10.2%	23.6%
Terminal Rates (c)	1/17 (6%)	0/22 (0%)	1/16 (6%)	4/19 (21%)
Day of First Observation	543	607	639	638
Life Table Tests (d)	P=0.066	P=0.440N	P=0.670	P=0.264
Logistic Regression Tests (d)	P=0.064	P=0.484N	P=0.664	P=0.250
Cochran-Armitage Trend Test (d)	P=0.065			
Fisher Exact Test (d)		P=0.500N	P=0.691N	P=0.219
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	5/60 (8%)	10/60 (17%)	8/60 (13%)	4/60 (7%)
Adjusted Rates (b)	27.2%	36.4%	41.2%	21.1%
Terminal Rates (c)	4/17 (24%)	6/22 (27%)	6/16 (38%)	4/19 (21%)
Day of First Observation	701	556	319	729
Life Table Tests (d)	P=0.218N	P=0.262	P=0.230	P=0.425N
Logistic Regression Tests (d)	P=0.198N	P=0.205	P=0.210	P=0.393N
Cochran-Armitage Trend Test (d)	P=0.211N			
Fisher Exact Test (d)		P=0.135	P=0.279	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(e) No P value is reported because no tumors were observed in the 600-ppm and control groups.
(f) Number of tumor-bearing animals/number of animals examined microscopically at the site

TABLE C4. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F1 MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	14/50	2/50	15/50
Methyl methacrylate	10/50	3/50	11/50
Propylene	7/50	9/50	16/50
1,2-Epoxybutane	7/49	5/49	11/49
Dichloromethane	3/50	2/50	5/50
Ethylene oxide	5/50	6/50	11/50
Bromoethane	5/50	2/50	7/50
Tetrachloroethylene	3/49	4/49	6/49
TOTAL	54/398 (13.6%)	33/398 (8.3%)	82/398 (20.6%)
SD (b)	7.45%	4.96%	8.03%
Range (c)			
High	14/50	9/50	16/50
Low	3/50	2/50	5/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	204/1,684 (12.1%)	80/1,684 (4.8%)	277/1,684 (16.4%)
SD (b)	6.18%	2.70%	6.91%
Range (c)			
High	14/50	5/49	17/50
Low	1/50	0/49	4/50

(a) Data as of May 12, 1988 for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	60	60	60	60
ALIMENTARY SYSTEM				
Esophagus	(59)	(60)	(60)	(57)
Inflammation, chronic		1 (2%)		
Gallbladder	(59)	(54)	(57)	(59)
Cyst	1 (2%)			
Infiltration cellular, lymphocytic	6 (10%)	8 (15%)	8 (14%)	7 (12%)
Inflammation, acute	1 (2%)	1 (2%)	2 (4%)	
Inflammation, chronic	1 (2%)			
Inflammation, chronic active		1 (2%)		
Intestine large	(60)	(60)	(60)	(60)
Anorectal junction, erosion		1 (2%)	1 (2%)	
Anorectal junction, inflammation, acute				1 (2%)
Anus, erosion			2 (3%)	1 (2%)
Anus, inflammation, acute			1 (2%)	
Anus, inflammation, chronic active		1 (2%)	1 (2%)	
Anus, ulcer		2 (3%)	2 (3%)	3 (5%)
Intestine large, cecum	(60)	(60)	(60)	(59)
Parasite metazoan			2 (3%)	3 (5%)
Intestine large, colon	(60)	(60)	(60)	(59)
Parasite metazoan	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Intestine large, rectum	(59)	(59)	(60)	(58)
Hemorrhage		1 (2%)		
Inflammation, acute			1 (2%)	
Inflammation, chronic			1 (2%)	
Ulcer	4 (7%)	2 (3%)	1 (2%)	
Anorectal junction, ulcer				1 (2%)
Intestine small, ileum	(60)	(60)	(60)	(60)
Amyloid deposition	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Intestine small, jejunum	(60)	(60)	(60)	(60)
Hyperplasia, lymphoid	1 (2%)			
Liver	(60)	(60)	(60)	(59)
Basophilic focus		2 (3%)		3 (5%)
Bile stasis	1 (2%)			
Cyst			1 (2%)	1 (2%)
Focal cellular change	1 (2%)			
Hematopoietic cell proliferation	21 (35%)	13 (22%)	17 (28%)	17 (29%)
Hyperplasia		1 (2%)		2 (3%)
Hypertrophy				1 (2%)
Infarct	1 (2%)	1 (2%)	1 (2%)	2 (3%)
Infiltration cellular, lymphocytic	2 (3%)	7 (12%)	10 (17%)	3 (5%)
Inflammation, acute	3 (5%)	1 (2%)	2 (3%)	2 (3%)
Inflammation, chronic	3 (5%)	1 (2%)	1 (2%)	
Necrosis	5 (8%)	6 (10%)	4 (7%)	9 (15%)
Bile duct, hyperplasia				1 (2%)
Caudate lobe, infarct		1 (2%)		
Centrilobular, fatty change	1 (2%)			
Periportal, inflammation, chronic	2 (3%)			
Serosa, inflammation, chronic				1 (2%)
Mesentery	(2)		(2)	(1)
Artery, inflammation, chronic			1 (50%)	
Artery, inflammation, chronic active	1 (50%)			

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ALIMENTARY SYSTEM *(Continued)*				
Pancreas	(60)	(60)	(60)	(59)
Cyst				1 (2%)
Fibrosis			1 (2%)	
Infiltration cellular, lymphocytic	11 (18%)	14 (23%)	18 (30%)	14 (24%)
Inflammation, acute		1 (2%)		
Inflammation, chronic			1 (2%)	
Inflammation, chronic active		1 (2%)		
Acinus, atrophy	1 (2%)	3 (5%)	1 (2%)	
Acinus, hyperplasia	1 (2%)		1 (2%)	
Salivary glands	(60)	(60)	(60)	(59)
Hemorrhage	1 (2%)			
Hyperplasia, glandular	1 (2%)			
Infiltration cellular		1 (2%)		
Infiltration cellular, lymphocytic	30 (50%)	36 (60%)	34 (57%)	30 (51%)
Mineralization				1 (2%)
Stomach, forestomach	(60)	(59)	(60)	(60)
Erosion				1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)	
Hyperplasia, squamous		7 (12%)	1 (2%)	
Hyperplasia, squamous, focal				1 (2%)
Infiltration cellular, lymphocytic	1 (2%)	3 (5%)	1 (2%)	1 (2%)
Inflammation, acute	4 (7%)	2 (3%)		2 (3%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active	2 (3%)		1 (2%)	
Ulcer	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(60)	(60)	(60)	(60)
Edema				2 (3%)
Erosion	4 (7%)	6 (10%)	6 (10%)	4 (7%)
Infiltration cellular, lymphocytic	14 (23%)	14 (23%)	17 (28%)	15 (25%)
Inflammation, acute	2 (3%)	2 (3%)		3 (5%)
Inflammation, chronic active	1 (2%)	1 (2%)		
Mucosa, dilatation	2 (3%)	6 (10%)	5 (8%)	13 (22%)
Mucosa, hyperplasia	1 (2%)			
Submucosa, edema			1 (2%)	
Tooth	(2)	(8)	(2)	(1)
Peridontal tissue, inflammation, chronic active		2 (25%)		
Pulp, inflammation, acute	2 (100%)	2 (25%)	2 (100%)	
Pulp, inflammation, chronic		1 (13%)		
Pulp, inflammation, chronic active		3 (38%)		
CARDIOVASCULAR SYSTEM				
Blood vessel	(59)	(60)	(60)	(60)
Aorta, inflammation, chronic				1 (2%)
Aorta, mineralization	1 (2%)			1 (2%)
Heart	(60)	(60)	(60)	(59)
Atrophy			1 (2%)	
Infiltration cellular, lymphocytic	9 (15%)	13 (22%)	9 (15%)	8 (14%)
Inflammation, acute		1 (2%)	1 (2%)	2 (3%)
Inflammation, chronic	5 (8%)	4 (7%)	1 (2%)	2 (3%)
Inflammation, chronic active			1 (2%)	2 (3%)
Mineralization			1 (2%)	
Atrium, thrombus				1 (2%)
Ventricle right, thrombus			1 (2%)	
ENDOCRINE SYSTEM				
Adrenal gland	(60)	(60)	(59)	(60)
Capsule, hyperplasia			1 (2%)	
Capsule, spindle cell, hyperplasia	59 (98%)	57 (95%)	53 (90%)	55 (92%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ENDOCRINE SYSTEM (Continued)				
Adrenal gland, cortex	(60)	(60)	(59)	(59)
Hyperplasia		3 (5%)	2 (3%)	
Hypertrophy	4 (7%)	3 (5%)	3 (5%)	3 (5%)
Pigmentation	8 (13%)	7 (12%)	10 (17%)	16 (27%)
Adrenal gland, medulla	(60)	(58)	(58)	(59)
Hyperplasia	1 (2%)	1 (2%)		
Islets, pancreatic	(60)	(60)	(60)	(58)
Hyperplasia		1 (2%)	1 (2%)	
Necrosis			1 (2%)	
Pituitary gland	(59)	(58)	(58)	(56)
Pars distalis, cyst	1 (2%)	1 (2%)		
Pars distalis, hyperplasia	2 (3%)	1 (2%)		
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(60)	(60)	(60)	(59)
Infiltration cellular, lymphocytic	8 (13%)	5 (8%)	2 (3%)	3 (5%)
Inflammation, acute				1 (2%)
C-cell, hyperplasia		1 (2%)		
Follicle, cyst	2 (3%)		1 (2%)	
Follicle, dilatation	3 (5%)	2 (3%)		3 (5%)
Follicle, hyperplasia	4 (7%)	5 (8%)	2 (3%)	3 (5%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(60)	(60)	(60)	(60)
Granuloma sperm	3 (5%)			1 (2%)
Infiltration cellular, lymphocytic	9 (15%)	3 (5%)	8 (13%)	4 (7%)
Inflammation, acute		1 (2%)	2 (3%)	3 (5%)
Inflammation, chronic			2 (3%)	1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)	4 (7%)
Penis	(17)	(21)	(17)	(21)
Abscess		3 (14%)	1 (6%)	
Concretion	1 (6%)			
Inflammation	1 (6%)	1 (5%)		1 (5%)
Inflammation, acute	16 (94%)	10 (48%)	13 (76%)	12 (57%)
Inflammation, chronic		2 (10%)		1 (5%)
Inflammation, chronic active		2 (10%)		1 (5%)
Necrosis		2 (10%)	4 (24%)	4 (19%)
Preputial gland	(12)	(9)	(10)	(11)
Abscess	4 (33%)	2 (22%)	3 (30%)	3 (27%)
Cyst	3 (25%)	2 (22%)	2 (20%)	2 (18%)
Infiltration cellular, lymphocytic		2 (22%)	1 (10%)	
Inflammation, acute	2 (17%)	1 (11%)		2 (18%)
Inflammation, chronic	3 (25%)	1 (11%)	2 (20%)	
Inflammation, chronic active	1 (8%)	1 (11%)	3 (30%)	2 (18%)
Prostate	(60)	(60)	(59)	(59)
Infiltration cellular, lymphocytic	8 (13%)	6 (10%)	16 (27%)	14 (24%)
Inflammation, acute	14 (23%)	13 (22%)	9 (15%)	12 (20%)
Inflammation, chronic	2 (3%)	2 (3%)		
Inflammation, chronic active	2 (3%)		3 (5%)	1 (2%)
Seminal vesicle	(4)	(4)	(4)	(6)
Dilatation		1 (25%)	2 (50%)	1 (17%)
Inflammation, chronic	1 (25%)	1 (25%)		
Inflammation, chronic active				1 (17%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
GENITAL SYSTEM (Continued)				
Testes	(60)	(60)	(60)	(60)
Atrophy	9 (15%)	12 (20%)	3 (5%)	3 (5%)
Granuloma sperm	2 (3%)			
Hemorrhage	1 (2%)			
Infiltration cellular, lymphocytic	1 (2%)			
Inflammation, acute			1 (2%)	2 (3%)
Mineralization		1 (2%)		
Interstitial cell, hyperplasia	1 (2%)	1 (2%)	2 (3%)	
Tunic, inflammation, chronic active			1 (2%)	
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(60)	(60)	(59)
Fibrosis			1 (2%)	1 (2%)
Inflammation, acute		1 (2%)		
Myeloid cell, hyperplasia	51 (85%)	48 (80%)	56 (93%)	44 (75%)
Lymph node	(60)	(60)	(59)	(59)
Congestion	2 (3%)		1 (2%)	
Hyperplasia, lymphoid	4 (7%)	3 (5%)	2 (3%)	1 (2%)
Inflammation, acute		1 (2%)	1 (2%)	1 (2%)
Iliac, hyperplasia, lymphoid	10 (17%)	4 (7%)	5 (8%)	4 (7%)
Iliac, hyperplasia, reticulum cell		1 (2%)		
Iliac, inflammation, acute		1 (2%)	1 (2%)	
Inguinal, hyperplasia, lymphoid	2 (3%)		3 (5%)	1 (2%)
Lumbar, hyperplasia, lymphoid			2 (3%)	
Mediastinal, hyperplasia, lymphoid	4 (7%)	1 (2%)	6 (10%)	5 (8%)
Mesenteric, autolysis				1 (2%)
Mesenteric, congestion	20 (33%)	14 (23%)	12 (20%)	11 (19%)
Mesenteric, hematopoietic cell proliferation				1 (2%)
Mesenteric, hemorrhage	1 (2%)	2 (3%)		
Mesenteric, hyperplasia, lymphoid	32 (53%)	24 (40%)	35 (59%)	27 (46%)
Mesenteric, inflammation, acute	4 (7%)	5 (8%)	3 (5%)	10 (17%)
Renal, congestion	1 (2%)			
Renal, hyperplasia, lymphoid	2 (3%)		2 (3%)	2 (3%)
Lymph node, mandibular	(53)	(52)	(54)	(51)
Autolysis				1 (2%)
Congestion			1 (2%)	
Hyperplasia, lymphoid	38 (72%)	40 (77%)	38 (70%)	32 (63%)
Inflammation, acute	1 (2%)			
Necrosis	1 (2%)			
Pigmentation			1 (2%)	
Spleen	(60)	(60)	(60)	(59)
Angiectasis	1 (2%)		2 (3%)	
Congestion		1 (2%)		
Hematopoietic cell proliferation	54 (90%)	50 (83%)	56 (93%)	47 (80%)
Hyperplasia, lymphoid	10 (17%)	7 (12%)	6 (10%)	5 (8%)
Hyperplasia, reticulum cell		1 (2%)		
Necrosis				2 (3%)
Pigmentation	4 (7%)	9 (15%)	11 (18%)	18 (31%)
Capsule, inflammation, chronic active			1 (2%)	
Thymus	(53)	(59)	(58)	(54)
Congestion		1 (2%)		
Cyst	3 (6%)		2 (3%)	1 (2%)
Ectopic parathyroid gland	1 (2%)			
Hyperplasia, lymphoid	2 (4%)	2 (3%)	4 (7%)	2 (4%)
Inflammation, chronic active		1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
INTEGUMENTARY SYSTEM				
Skin	(60)	(60)	(60)	(58)
Alopecia	4 (7%)	5 (8%)	3 (5%)	5 (9%)
Inflammation, acute	1 (2%)	1 (2%)		
Inflammation, chronic	2 (3%)	1 (2%)	1 (2%)	
Ulcer	3 (5%)	1 (2%)	2 (3%)	4 (7%)
Abdominal, abscess		1 (2%)		
Abdominal, thoracic, alopecia		1 (2%)		
Foot, ulcer		1 (2%)	2 (3%)	1 (2%)
Head, abscess		1 (2%)		1 (2%)
Head, inflammation, acute	2 (3%)	1 (2%)		
Head, inflammation, chronic	3 (5%)		1 (2%)	
Head, ulcer				1 (2%)
Inguinal, abscess	1 (2%)			
Inguinal, inflammation, acute			1 (2%)	
Inguinal, ulcer	1 (2%)	4 (7%)	2 (3%)	
Neck, abscess			1 (2%)	
Neck, alopecia				1 (2%)
Prepuce, abscess	2 (3%)	2 (3%)		
Prepuce, inflammation, acute				1 (2%)
Prepuce, inflammation, chronic active		1 (2%)		1 (2%)
Prepuce, ulcer	9 (15%)	14 (23%)	8 (13%)	10 (17%)
Scrotal, abscess	5 (8%)		1 (2%)	1 (2%)
Scrotal, inflammation, acute		1 (2%)		
Scrotal, inflammation, chronic active			1 (2%)	
Scrotal, ulcer	16 (27%)	9 (15%)	16 (27%)	8 (14%)
Subcutaneous tissue, edema		1 (2%)		1 (2%)
Subcutaneous tissue, inflammation, acute	2 (3%)	1 (2%)		
Subcutaneous tissue, inflammation, chronic	1 (2%)			
Subcutaneous tissue, head, abscess	2 (3%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, head, granuloma		1 (2%)		
Subcutaneous tissue, head, inflammation, acute	1 (2%)			
Subcutaneous tissue, head, inflammation, chronic active		1 (2%)		
Tail, inflammation, acute	1 (2%)			
Tail, inflammation, chronic			1 (2%)	
Tail, necrosis	1 (2%)			
Tail, ulcer		1 (2%)	1 (2%)	
Thoracic, alopecia	1 (2%)			
Ventral, alopecia	2 (3%)	2 (3%)		
MUSCULOSKELETAL SYSTEM				
Bone	(60)	(60)	(60)	(60)
Cranium, inflammation, chronic active		1 (2%)		1 (2%)
Femur, hyperostosis	1 (2%)			1 (2%)
Tibia, fracture				1 (2%)
Skeletal muscle		(2)	(6)	(3)
Abscess			1 (17%)	
Inflammation, acute				1 (33%)
Inflammation, chronic				1 (33%)
Inflammation, chronic active				1 (33%)
Head, abscess			4 (67%)	
Head, inflammation, acute		1 (50%)		
Head, inflammation, chronic active			1 (17%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
NERVOUS SYSTEM				
Brain	(60)	(60)	(60)	(60)
Abscess				1 (2%)
Compression			1 (2%)	
Hemorrhage	2 (3%)	3 (5%)	2 (3%)	1 (2%)
Infiltration cellular, lymphocytic	1 (2%)			
Mineralization	40 (67%)	35 (58%)	41 (68%)	35 (58%)
RESPIRATORY SYSTEM				
Lung	(60)	(60)	(60)	(60)
Abscess				1 (2%)
Congestion	11 (18%)	12 (20%)	5 (8%)	8 (13%)
Granuloma			2 (3%)	
Hemorrhage	6 (10%)	11 (18%)	16 (27%)	3 (5%)
Infiltration cellular, lymphocytic	50 (83%)	54 (90%)	55 (92%)	52 (87%)
Inflammation, acute			1 (2%)	
Mineralization	2 (3%)			
Alveolar epithelium, hyperplasia	1 (2%)		2 (3%)	1 (2%)
Alveolus, infiltration cellular, histiocytic	3 (5%)	1 (2%)	2 (3%)	3 (5%)
Arteriole, inflammation, acute			1 (2%)	
Artery, inflammation, acute			1 (2%)	
Interstitium, inflammation, acute	5 (8%)	1 (2%)	3 (5%)	4 (7%)
Interstitium, inflammation, chronic	1 (2%)			
Peribronchiolar, inflammation, acute	1 (2%)			
Peribronchiolar, inflammation, chronic	2 (3%)	1 (2%)		
Peribronchiolar, inflammation, chronic active				1 (2%)
Perivascular, inflammation, acute		1 (2%)		
Nose	(59)	(59)	(60)	(59)
Lumen, hemorrhage	36 (61%)	25 (42%)	40 (67%)	29 (49%)
Mucosa, inflammation, acute	1 (2%)	3 (5%)	1 (2%)	6 (10%)
Nasolacrimal duct, hemorrhage	2 (3%)	1 (2%)		
Nasolacrimal duct, inflammation, acute	1 (2%)	4 (7%)	5 (8%)	
Olfactory epithelium, degeneration	41 (69%)	11 (19%)	27 (45%)	30 (51%)
Olfactory epithelium, metaplasia				1 (2%)
Respiratory epithelium, degeneration	7 (12%)	1 (2%)	8 (13%)	4 (7%)
Respiratory epithelium, inflammation, acute		1 (2%)		
Septum, inflammation, acute			1 (2%)	
Septum, inflammation, chronic active		1 (2%)		
Sinus, inflammation, acute				1 (2%)
Turbinate, congestion			1 (2%)	2 (3%)
Turbinate, inflammation, acute	1 (2%)			
Vomeronasal organ, congestion		1 (2%)		
Vomeronasal organ, inflammation, acute		1 (2%)	2 (3%)	
Trachea	(60)	(60)	(60)	(59)
Inflammation, chronic active			1 (2%)	
Glands, inflammation, acute		3 (5%)		
Mucosa, erosion	1 (2%)			
SPECIAL SENSES SYSTEM				
Harderian gland		(3)	(1)	(3)
Cyst				1 (33%)
URINARY SYSTEM				
Kidney	(60)	(60)	(60)	(59)
Abscess		1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)			
Cyst	1 (2%)			
Hemorrhage			1 (2%)	
Hydronephrosis		1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
URINARY SYSTEM				
Kidney (Continued)	(60)	(60)	(60)	(59)
Infiltration cellular, lymphocytic	53 (88%)	52 (87%)	52 (87%)	48 (81%)
Inflammation, acute	4 (7%)	3 (5%)	3 (5%)	3 (5%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active		1 (2%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)	
Capsule, inflammation, chronic				1 (2%)
Cortex, cyst	2 (3%)	2 (3%)		2 (3%)
Pelvis, calculus micro observation only				1 (2%)
Pelvis, dilatation	14 (23%)	10 (17%)	9 (15%)	4 (7%)
Pelvis, hemorrhage		1 (2%)		1 (2%)
Pelvis, inflammation, acute	7 (12%)	3 (5%)	5 (8%)	9 (15%)
Pelvis, inflammation, chronic	1 (2%)			
Pelvis, inflammation, chronic active	1 (2%)			1 (2%)
Renal tubule, casts protein	4 (7%)	6 (10%)	4 (7%)	2 (3%)
Renal tubule, cyst	2 (3%)		1 (2%)	
Renal tubule, dilatation	13 (22%)	17 (28%)	15 (25%)	17 (29%)
Renal tubule, hyperplasia	1 (2%)	3 (5%)	1 (2%)	
Renal tubule, mineralization	2 (3%)	6 (10%)	1 (2%)	
Renal tubule, necrosis	6 (10%)	12 (20%)	9 (15%)	12 (20%)
Renal tubule, regeneration	36 (60%)	30 (50%)	29 (48%)	21 (36%)
Ureter	(8)	(1)	(3)	
Dilatation	3 (38%)	1 (100%)	3 (100%)	
Inflammation, acute	1 (13%)			
Urethra	(5)	(6)	(1)	(3)
Calculus micro observation only	3 (60%)	4 (67%)		1 (33%)
Inflammation, acute	1 (20%)	1 (17%)	1 (100%)	1 (33%)
Inflammation, chronic	1 (20%)			
Bulbourethral gland, inflammation, acute		1 (17%)		
Urinary bladder	(60)	(60)	(60)	(59)
Angiectasis	2 (3%)	1 (2%)		
Calculus gross observation	1 (2%)	1 (2%)		2 (3%)
Calculus micro observation only	1 (2%)			2 (3%)
Congestion		1 (2%)		
Ectasia	19 (32%)	10 (17%)	15 (25%)	13 (22%)
Hemorrhage	1 (2%)			
Infiltration cellular, lymphocytic	27 (45%)	25 (42%)	36 (60%)	31 (53%)
Inflammation, acute	10 (17%)	8 (13%)	7 (12%)	11 (19%)
Inflammation, chronic	1 (2%)	3 (5%)		
Inflammation, chronic active	6 (10%)		1 (2%)	4 (7%)

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	47
ALIMENTARY SYSTEM				
Gallbladder	(49)	(49)	(50)	(45)
Lymphoma malignant mixed	4 (8%)	3 (6%)	1 (2%)	
Lymphoma malignant undifferentiated cell type			2 (4%)	
Intestine large, cecum	(49)	(50)	(50)	(47)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	1 (2%)	1 (2%)		
Intestine large, rectum	(50)	(50)	(50)	(45)
Lymphoma malignant lymphocytic				1 (2%)
Intestine small, duodenum	(49)	(50)	(50)	(47)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed			1 (2%)	
Lymphoma malignant undifferentiated cell type			2 (4%)	
Intestine small, jejunum	(49)	(50)	(50)	(47)
Lymphoma malignant mixed	3 (6%)	1 (2%)		
Lymphoma malignant undifferentiated cell type				1 (2%)
Liver	(49)	(50)	(50)	(47)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)			
Hepatocellular carcinoma	4 (8%)	2 (4%)	2 (4%)	7 (15%)
Hepatocellular adenoma	3 (6%)	7 (14%)	6 (12%)	7 (15%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant histiocytic			1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	2 (4%)			2 (4%)
Lymphoma malignant mixed	8 (16%)	6 (12%)	8 (16%)	
Lymphoma malignant undifferentiated cell type			3 (6%)	1 (2%)
Mesentery	*(50)	*(50)	*(50)	*(47)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			
Lymphoma malignant			1 (2%)	
Lymphoma malignant mixed	3 (6%)	2 (4%)	2 (4%)	
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
Pancreas	(50)	(50)	(50)	(47)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	6 (12%)	3 (6%)	3 (6%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
Salivary glands	(50)	(50)	(50)	(46)
Lymphoma malignant histiocytic	1 (2%)			
Lymphoma malignant lymphocytic	2 (4%)			1 (2%)
Lymphoma malignant mixed	4 (8%)	4 (8%)		
Lymphoma malignant undifferentiated cell type			1 (2%)	
Stomach	(50)	(50)	(50)	(47)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)			
Stomach, forestomach	(50)	(49)	(50)	(47)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	3 (6%)	1 (2%)	2 (4%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
Papilloma squamous	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Glandular, lymphoma malignant mixed		1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ALIMENTARY SYSTEM (Continued)				
Stomach, glandular	(49)	(50)	(50)	(47)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	6 (12%)	2 (4%)	2 (4%)	1 (2%)
Lymphoma malignant undifferentiated cell type			2 (4%)	
CARDIOVASCULAR SYSTEM				
Blood vessel	(50)	(50)	(50)	(47)
Lymphoma malignant lymphocytic	1 (2%)			
Heart	(50)	(50)	(50)	(47)
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, metastatic, ovary				1 (2%)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	1 (2%)	3 (6%)	1 (2%)	
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(49)	(50)	(50)	(47)
Adenoma			1 (2%)	1 (2%)
Lymphoma malignant mixed	1 (2%)			
Lymphoma malignant undifferentiated cell type			1 (2%)	
Capsule, lymphoma malignant undifferentiated cell type			1 (2%)	
Adrenal gland, medulla	(49)	(50)	(49)	(47)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma, NOS	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Pituitary gland	(49)	(48)	(49)	(46)
Pars distalis, adenoma	12 (24%)	19 (40%)	21 (43%)	15 (33%)
Pars distalis, lymphoma malignant mixed		1 (2%)		
Pars intermedia, adenoma		1 (2%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(47)
Lymphoma malignant mixed		1 (2%)		
Follicle, adenocarcinoma	1 (2%)			
Follicle, adenoma			4 (8%)	
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Ovary	(50)	(49)	(50)	(47)
Granulosa cell tumor benign		1 (2%)		
Hemangioma	1 (2%)			1 (2%)
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, metastatic				1 (2%)
Histiocytic sarcoma				1 (2%)
Luteoma	1 (2%)			
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	4 (8%)	1 (2%)	2 (4%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
Uterus	(50)	(50)	(50)	(47)
Adenocarcinoma		1 (2%)		
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma				1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
GENITAL SYSTEM				
Uterus (Continued)	(50)	(50)	(50)	(47)
Leiomyoma		1 (2%)		
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	2 (4%)	1 (2%)	1 (2%)	
Lymphoma malignant undifferentiated cell type			1 (2%)	
Endometrium, polyp stromal	3 (6%)	2 (4%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM				
Blood	*(50)	*(50)	*(50)	*(47)
Leukemia		1 (2%)		
Bone marrow	(50)	(50)	(50)	(47)
Hemangioma		1 (2%)		
Hemangiosarcoma, metastatic, ovary				1 (2%)
Hemangiosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma, metastatic, spleen				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	2 (4%)	1 (2%)	1 (2%)	
Lymph node	(48)	(49)	(50)	(46)
Adenocarcinoma, metastatic, uterus		1 (2%)		
Lymphoma malignant mixed	3 (6%)	2 (4%)	1 (2%)	
Lymphoma malignant undifferentiated cell type			2 (4%)	1 (2%)
Axillary, lymphoma malignant mixed	1 (2%)			
Axillary, lymphoma malignant undifferentiated cell type				1 (2%)
Bronchial, lymphoma malignant mixed	1 (2%)			
Iliac, histiocytic sarcoma			1 (2%)	1 (2%)
Iliac, lymphoma malignant histiocytic				1 (2%)
Iliac, lymphoma malignant mixed	3 (6%)	3 (6%)	5 (10%)	3 (7%)
Iliac, lymphoma malignant undifferentiated cell type			2 (4%)	
Mediastinal, lymphoma malignant histiocytic				1 (2%)
Mediastinal, lymphoma malignant lymphocytic				1 (2%)
Mediastinal, lymphoma malignant mixed	5 (10%)	2 (4%)	4 (8%)	1 (2%)
Mediastinal, lymphoma malignant undifferentiated cell type			1 (2%)	
Mesenteric, histiocytic sarcoma			2 (4%)	
Mesenteric, lymphoma malignant histiocytic				1 (2%)
Mesenteric, lymphoma malignant lymphocytic	2 (4%)			2 (4%)
Mesenteric, lymphoma malignant mixed	14 (29%)	8 (16%)	10 (20%)	6 (13%)
Mesenteric, lymphoma malignant undifferentiated cell type			2 (4%)	2 (4%)
Mesenteric, osteosarcoma, metastatic, uncertain primary site				1 (2%)
Renal, histiocytic sarcoma			2 (4%)	
Renal, lymphoma malignant histiocytic				1 (2%)
Renal, lymphoma malignant lymphocytic				1 (2%)
Renal, lymphoma malignant mixed	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Renal, lymphoma malignant undifferentiated cell type			2 (4%)	
Lymph node, mandibular	(47)	(48)	(50)	(43)
Histiocytic sarcoma			1 (2%)	
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			2 (5%)
Lymphoma malignant mixed	11 (23%)	6 (13%)	5 (10%)	4 (9%)
Lymphoma malignant undifferentiated cell type			1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM (Continued)				
Spleen	(50)	(50)	(49)	(47)
Adenocarcinoma, metastatic, uterus		1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)		2 (4%)
Hemangiosarcoma, metastatic, uterus				1 (2%)
Histiocytic sarcoma			2 (4%)	1 (2%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			2 (4%)
Lymphoma malignant mixed	18 (36%)	9 (18%)	11 (22%)	6 (13%)
Lymphoma malignant undifferentiated cell type			3 (6%)	2 (4%)
Thymus	(46)	(48)	(48)	(47)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	2 (4%)			2 (4%)
Lymphoma malignant mixed	15 (33%)	8 (17%)	4 (8%)	1 (2%)
Lymphoma malignant undifferentiated cell type			1 (2%)	1 (2%)
INTEGUMENTARY SYSTEM				
Mammary gland	(49)	(50)	(48)	(46)
Adenoacanthoma		1 (2%)		
Adenocarcinoma	2 (4%)		2 (4%)	
Carcinoma				1 (2%)
Skin	(50)	(50)	(50)	(47)
Papilloma squamous				1 (2%)
Subcutaneous tissue, fibrosarcoma			2 (4%)	1 (2%)
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(50)	*(50)	*(50)	*(47)
Head, sarcoma, deep invasion		1 (2%)		
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(47)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	2 (4%)	1 (2%)	2 (4%)	
Choroid plexus, lymphoma malignant mixed		1 (2%)		
Meninges, sarcoma, metastatic		1 (2%)		
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(47)
Alveolar/bronchiolar adenoma	5 (10%)		3 (6%)	4 (9%)
Alveolar/bronchiolar carcinoma		3 (6%)	1 (2%)	3 (6%)
Carcinoma, metastatic				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			2 (4%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant histiocytic	1 (2%)			1 (2%)
Lymphoma malignant lymphocytic	2 (4%)			2 (4%)
Lymphoma malignant mixed	10 (20%)	8 (16%)	8 (16%)	1 (2%)
Lymphoma malignant undifferentiated cell type			2 (4%)	
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland	*(50)	*(50)	*(50)	*(47)
Adenoma		2 (4%)	1 (2%)	1 (2%)
Carcinoma				1 (2%)
Bilateral, adenocarcinoma			1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(47)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)		1 (2%)
Lymphoma malignant mixed	11 (22%)	5 (10%)	7 (14%)	3 (6%)
Lymphoma malignant undifferentiated cell type			1 (2%)	1 (2%)
Osteosarcoma, metastatic, uncertain primary site				1 (2%)
Urinary bladder	(50)	(50)	(50)	(47)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic	2 (4%)			1 (2%)
Lymphoma malignant mixed	10 (20%)	5 (10%)	4 (8%)	1 (2%)
Lymphoma malignant undifferentiated cell type			1 (2%)	
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(47)
Lymphoma malignant mixed	20 (40%)	10 (20%)	13 (26%)	6 (13%)
Hemangiosarcoma	2 (4%)	2 (4%)	1 (2%)	6 (13%)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)		2 (4%)
Lymphoma malignant histiocytic	2 (4%)		1 (2%)	1 (2%)
Hemangioma	2 (4%)	1 (2%)		2 (4%)
Leukemia		1 (2%)		
Lymphoma malignant			1 (2%)	
Lymphoma malignant undifferentiated cell			3 (6%)	2 (4%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	60	60	60	60
Interval sacrifice	10	10	10	10
Terminal sacrifice	30	33	23	32
Dead	11	6	14	9
Moribund	8	8	11	3
Accident	1	3		1
Natural death			2	2
Missing				3
TUMOR SUMMARY				
Total animals with primary neoplasms **	33	36	42	38
Total primary neoplasms	63	59	81	76
Total animals with benign neoplasms	19	28	29	29
Total benign neoplasms	29	35	39	37
Total animals with malignant neoplasms	26	17	27	26
Total malignant neoplasms	33	23	41	37
Total animals with secondary neoplasms ***	1	2	1	8
Total secondary neoplasms	1	3	1	13
Total animals with malignant neoplasms-- uncertain primary site				1
Total animals with neoplasms-- uncertain benign or malignant	1	1	1	2
Total uncertain neoplasms	1	1	1	2

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: CHAMBER CONTROL

WEEKS ON STUDY	001	050	054	057	067	080	090	091	091	091	094	098	098	099	102	102	102	103	103	104	105	105	105	105	105
CARCASS ID	1131	1121	0831	1181	1091	0981	0631	0891	0771	0901	0961	1151	1051	0991	0881	0841	1031	0641	0701	0741	0621	0721	0811	0851	0911
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X						X						
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									X
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma												X													
Hepatocellular carcinoma								X		X															
Hepatocellular adenoma																									X
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed													X		X				X	X					
Mesentery			+																+	+					
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																			X	X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X				X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed															X										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed							X								X				X						
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X						
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, NOS																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	+	+	M	+	+	+	M	M	+	M	+	M	M	M	+	+	+	+	+	M
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X					X									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle, adenocarcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland																	+								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Luteoma																									
Lymphoma malignant mixed							X			X					X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed							X																		
Endometrium, polyp stromal																									
Vagina								+																	

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue
M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	1021	1161	1191	0781	0791	0921	0941	1041	1061	1071	0711	1001	1081	1171	1201	0651	0661	0731	0861	0931	0681	0761	0821	0871	1151	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X	X																			4
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X							X													3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																									X	1
Hemangiosarcoma																										1
Hepatocellular carcinoma					X							X														4
Hepatocellular adenoma						X											X									3
Lymphoma malignant lymphocytic														X				X								2
Lymphoma malignant mixed					X	X	X	X																		8
Mesentery														+							+					5
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed																					X					3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed								X	X										X		X					6
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																				X						1
Lymphoma malignant lymphocytic														X				X								2
Lymphoma malignant mixed					X					X									X							4
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X												1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed							X												X							3
Papilloma squamous							X													X				X		3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed						X				X									X							6
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																		X								1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed										X																1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, NOS														X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X				X		X			X				X			X	X		X		X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenocarcinoma					X																					1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma										X																1
Luteoma									X																	1
Lymphoma malignant mixed									X																	4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed									X																	2
Endometrium, polyp stromal											X		X		X											3
Vagina																										1

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

WEEKS ON STUDY	001	050	054	057	067	080	090	091	091	091	094	098	098	099	102	102	102	103	103	104	105	105	105	105	105
CARCASS ID	1131	1121	0831	1181	1091	0981	0631	0891	0771	0901	0961	1111	1051	0991	0881	0841	1031	0641	0701	0741	0621	0721	0811	0851	0911
HEMATOPOIETIC SYSTEM																									
Blood							+																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									X
Lymph node	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Axillary, lymphoma malignant mixed																				X					
Bronchial, lymphoma malignant mixed															X										
Iliac, lymphoma malignant mixed															X					X					X
Mediastinal, lymphoma malignant mixed													X		X					X					X
Mesenteric, lymphoma malignant lymphocytic																									
Mesenteric, lymphoma malignant mixed										X			X		X				X	X				X	X
Renal, lymphoma malignant mixed															X					X					X
Lymph node, mandibular	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed													X		X				X					X	X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed										X			X		X				X	X				X	X
Thymus	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed							X						X		X				X	X				X	X
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										X															
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X				X									
Hepatocellular carcinoma, metastatic, liver										X															
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed							X						X		X				X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed													X		X				X	X				X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed													X							X				X	X

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	1021	1161	1191	0781	0791	0921	0941	1041	1061	1071	0711	1001	1081	1171	1201	0651	0661	0731	0861	0931	0681	0761	0821	0871	1151	
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed								X																		2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed									X								X									3
Axillary, lymphoma malignant mixed																										1
Bronchial, lymphoma malignant mixed																										1
Iliac, lymphoma malignant mixed																										3
Mediastinal, lymphoma mal mixed					X																					5
Mesenteric, lymphoma malignant lymphocytic														X				X								2
Mesenteric, lymphoma malignant mixed						X	X	X	X	X									X		X					14
Renal, lymphoma malignant mixed																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																		X								1
Lymphoma malignant mixed					X	X	X		X										X		X					11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																					X					1
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed					X	X	X	X	X	X	X						X		X	X	X					18
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic														X				X								2
Lymphoma malignant mixed					X	X	X			X	X						X		X		X					15
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma												X														2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed									X																	2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X								X									5
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic							X																			1
Lymphoma malignant lymphocytic														X				X								2
Lymphoma malignant mixed					X	X			X	X									X		X					10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
None																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed						X			X	X	X								X		X					11
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X				X								2
Lymphoma malignant mixed						X	X		X	X									X	X						10

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 120 ppm

WEEKS ON STUDY	002	056	056	056	062	065	066	069	077	086	093	094	098	098	099	099	104	105	105	105	105	105	105	105	105
CARCASS ID	4771	4691	4701	4711	4561	4481	4761	4451	4541	4491	4331	4741	4591	4361	4791	4351	4681	4271	4291	4411	4621	4671	4211	4261	4431
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X			X								
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X						X											
Hepatocellular adenoma													X			X									
Lymphoma malignant mixed													X	X			X								
Mesentery													+	+											
Lymphoma malignant mixed													X	X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X								X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X	X			X								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Papilloma squamous																									
Glandular, lymphoma malignant mixed														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X	X			X								
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant										X															
Pheochromocytoma, NOS																									
Islets, pancreatic	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	M	M
Pituitary gland	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X	X	X	X			X							X
Pars distalis, lymphoma malignant mixed													X												
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign									X																
Lymphoma malignant mixed														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X													
Hemangiosarcoma																						X			
Leiomyoma																									
Lymphoma malignant mixed																	X								
Endometrium, polyp stromal																	X								

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	4441	4501	4631	4751	4221	4231	4311	4421	4461	4551	4651	4391	4531	4571	4611	4641	4721	4781	4241	4251	4281	4301	4581	4661	4801	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																				X						3
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma		X					X		X			X							X							7
Lymphoma malignant mixed		X																	X	X						6
Mesentery																										2
Lymphoma malignant mixed																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																			X							3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																				X						4
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																				X						1
Papilloma squamous												X														1
Glandular, lymphoma malignant mixed																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																				X						2
Tooth																				+						1
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma, NOS																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	M	M	M	+	M	M	M	M	+	+	M	M	M	M	M	M	M	+	+	M	M	+	M	M	12
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X	X	X	X	X		X	X			X				X		X		X	X		X	19
Pars distalis, lymphoma malignant mixed																										1
Pars intermedia, adenoma																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor benign																										1
Lymphoma malignant mixed																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Hemangiosarcoma																										1
Leiomyoma				X																						1
Lymphoma malignant mixed																										1
Endometrium, polyp [illegible]								X																		2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	002	056	056	056	062	065	066	069	077	086	093	094	098	098	099	099	104	105	105	105	105	105	105	105	105
CARCASS ID	4771	4691	4701	4711	4561	4481	4761	4451	4541	4491	4331	4741	4591	4361	4791	4351	4681	4271	4291	4411	4621	4671	4211	4261	4431
HEMATOPOIETIC SYSTEM																									
Blood																									
Leukemia																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymphoma malignant mixed																									
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus												X													
Lymphoma malignant mixed																						X			
Iliac, lymphoma malignant mixed														X			X						X		
Mediastinal, lymphoma malignant mixed													X				X								
Mesenteric, lymphoma malignant mixed										X			X	X			X						X		
Renal, lymphoma malignant mixed														X			X						X		
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X	X			X					X	X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus												X													
Hemangiosarcoma																									
Lymphoma malignant mixed													X	X			X					X	X		
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X	X			X					X	X		
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoacanthoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Head, sarcoma, deep invasion									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Choroid plexus, lymphoma malignant mixed														X											
Meninges, sarcoma, metastatic									X																
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma														X											
Lymphoma malignant mixed													X	X			X					X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+																
Harderian gland												+													
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																	X								
Lymphoma malignant mixed														X								X	X		
Ureter												+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X	X									X		

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 120 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	4441	4501	4631	4751	4221	4231	4311	4421	4461	4551	4651	4391	4531	4571	4611	4641	4721	4781	4241	4251	4281	4301	4581	4661	4801	
HEMATOPOIETIC SYSTEM																										
Blood		+																								1
Leukemia		X																								1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma	X																									1
Lymphoma malignant mixed		X																								1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, metastatic, uterus																										1
Lymphoma malignant mixed																				X						2
Iliac, lymphoma malignant mixed																										3
Mediastinal, lymphoma mal mixed																										2
Mesenteric, lymphoma malignant mixed														X					X	X						8
Renal, lymphoma malignant mixed																										3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																				X						6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Hemangiosarcoma						X																				1
Lymphoma malignant mixed		X												X					X	X						9
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed														X					X	X						8
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoacanthoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Head, sarcoma, deep invasion																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																			X							1
Choroid plexus, lymphoma malignant mixed																										1
Meninges, sarcoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma			X												X											3
Lymphoma malignant mixed		X												X					X	X						8
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										1
Harderian gland										+														+		3
Adenoma										X														X		2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																			X	X						5
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																			X	X						5

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 600 ppm

WEEKS ON STUDY	024	057	073	073	074	081	083	086	086	087	090	090	092	093	094	095	095	096	100	101	102	102	102	102	102
CARCASS ID	1831	1921	2261	2061	2041	2141	1961	2021	2311	1851	2221	2181	2121	2331	2381	2161	2401	2131	2151	2071	1991	2201	2241	1841	2341
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed															X										
Lymphoma malignant undifferentiated cell type										X	X														
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												
Lymphoma malignant undifferentiated cell type										X	X														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X																		
Hepatocellular adenoma				X																					
Histiocytic sarcoma																									
Lymphoma malignant histiocytic																								X	
Lymphoma malignant mixed									X				X		X								X		X
Lymphoma malignant undifferentiated cell type										X	X									X					
Mesentery										+								+							
Lymphoma malignant										X															
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X						X						X
Lymphoma malignant undifferentiated cell type											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type											X														
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												
Lymphoma malignant undifferentiated cell type											X														
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												X
Lymphoma malignant undifferentiated cell type											X									X					
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed																							X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Lymphoma malignant undifferentiated cell type										X															
Capsule, lymphoma malignant undifferentiated cell type											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pheochromocytoma NOS																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	M	+	M	+	+	M	M	M	M	+	+	M	+	M	+	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X					X				X	X				X		X	X	X	X	X			X
Pars intermedia, adenoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicle adenoma												X				X	X								
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X												X
Lymphoma malignant undifferentiated cell type											X														
Oviduct																	+								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																								X	
Lymphoma malignant mixed																									X
Lymphoma malignant undifferentiated cell type											X														
Endometrium, polyp stromal																									X
Vagina			+																						

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	2011	1951	2031	2111	2361	2391	1811	1821	2081	2171	2231	1871	1901	2041	2211	2271	1911	1941	2291	2371	1861	1891	1931	2101	2321	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										2
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																					X					2
Hepatocellular adenoma				X		X		X		X													X			6
Histiocytic sarcoma													X													1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																		X		X					X	8
Lymphoma malignant undifferentiated cell type																										3
Mesentery		+															+									4
Lymphoma malignant																										1
Lymphoma malignant mixed		X															X									2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										3
Lymphoma malignant undifferentiated cell type																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																				X						2
Lymphoma malignant undifferentiated cell type																										1
Papilloma squamous		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type																										2
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Lymphoma malignant undifferentiated cell type																										1
Capsule, lymphoma malignant undifferentiated cell type																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, NOS																		X								1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	+	+	18
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X		X		X	X			X		X				X	X							X	X	21
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicle, adenoma																			X							4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																										1
Ovary	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type																										1
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1
Endometrium, polyp stromal																										1
Vagina																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	024	057	073	073	074	081	083	086	086	087	090	090	092	093	094	095	095	096	100	101	102	102	102	102	102
CARCASS ID	1831	1921	2261	2061	2001	2141	1961	2021	2311	1851	2221	2181	2121	2331	2381	2161	2401	2131	2151	2071	1991	2201	2241	1841	2341
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skin																					X				
Lymphoma malignant mixed																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
Lymphoma malignant undifferentiated cell type										X										X					
Iliac, histiocytic sarcoma																									
Iliac, lymphoma malignant mixed													X		X				X						X
Iliac, lymphoma malignant undifferentiated cell type											X									X					
Mediastinal, lymphoma malignant mixed															X										X
Mediastinal, lymphoma malignant undifferentiated cell type											X														
Mesenteric, histiocytic sarcoma																									
Mesenteric, lymphoma malignant mixed		X											X		X				X						X
Mesenteric, lymphoma malignant undifferentiated cell type											X									X					
Renal, histiocytic sarcoma																									
Renal, lymphoma malignant mixed													X						X						
Renal, lymphoma malignant undifferentiated cell type											X									X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed													X		X				X						
Lymphoma malignant undifferentiated cell type											X														
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed		X							X				X						X				X		X
Lymphoma malignant undifferentiated cell type										X	X									X					
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed													X						X						X
Lymphoma malignant undifferentiated cell type											X														
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma																X						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																					X				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X		X			
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma																									
Lymphoma malignant mixed									X				X		X				X				X		X
Lymphoma malignant undifferentiated cell type										X	X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
Bilateral, adenocarcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant mixed													X		X				X						X
Lymphoma malignant undifferentiated cell type											X														
Ureter					+																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X		X
Lymphoma malignant undifferentiated cell type											X														

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 ppm (Continued)

WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	2011	1951	2031	2111	2361	2391	1811	1821	2081	2171	2231	1871	1901	2041	2211	2271	1911	1941	2291	2371	1861	1891	1931	2101	2321	
HEMATOPOIETIC SYSTEM																										
Blood	+																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skin																										1
Lymphoma malignant mixed																		X								1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										2
Iliac, histiocytic sarcoma													X													1
Iliac, lymphoma malignant mixed																				X						5
Iliac, lymphoma malignant undifferentiated cell type																										2
Mediastinal, lymphoma mal. mixed		X																X								4
Mediastinal, lymphoma malignant undifferentiated cell type																										1
Mesenteric, histiocytic sarcoma											X		X													2
Mesenteric, lymphoma malignant mixed		X															X	X		X					X	10
Mesenteric, lymphoma malignant undifferentiated cell type																										2
Renal, histiocytic sarcoma											X		X													2
Renal, lymphoma malignant mixed																				X						3
Renal, lymphoma malignant undifferentiated cell type																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Lymphoma malignant mixed		X																		X						5
Lymphoma malignant undifferentiated cell type																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma											X		X													2
Lymphoma malignant mixed		X															X	X		X		X				11
Lymphoma malignant undifferentiated cell type																										3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymphoma malignant mixed		X																								4
Lymphoma malignant undifferentiated cell type																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma	X											X														2
Subcutaneous tissue, hemangiosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle		+																	+							2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																	X									2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											3
Alveolar/bronchiolar carcinoma		X																								1
Histiocytic sarcoma													X													1
Lymphoma malignant mixed		X																		X						8
Lymphoma malignant undifferentiated cell type																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland					+			+																		2
Adenoma					X																					1
Bilateral, adenocarcinoma								X																		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Lymphoma malignant mixed																		X		X		X				7
Lymphoma malignant undifferentiated cell type																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																	X	X								4
Lymphoma malignant undifferentiated cell type																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE: 1,200 ppm

WEEKS ON STUDY	001	012	033	058	070	070	070	075	075	085	085	086	089	096	100	102	103	103	105	105	105	105	105	105	105
CARCASS ID	3581	3341	3531	3171	3501	3511	3521	3471	3261	3381	3071	3481	3391	3281	3571	3541	3491	3111	3041	3091	3151	3221	3271	3371	3451
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Intestine large, colon	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	M	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Intestine small	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Intestine small, ileum	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type														X											
Liver	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X			X					X							
Hepatocellular adenoma								X									X					X			
Histiocytic sarcoma																X									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant undifferentiated cell type														X											
Mesentery										+					+										
Hepatocellular carcinoma, metastatic, liver										X															
Osteosarcoma, metastatic, uncertain primary site															X										
Pancreas	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Salivary glands	+	+	+	+				+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic																									
Stomach	+	+	+	+				+	+	+	+	+	+	·	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Papilloma squamous																									
Stomach, glandular	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									
CARDIOVASCULAR SYSTEM																									
Blood vessel	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, ovary														X											
Lymphoma malignant lymphocytic																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Adrenal gland, medulla	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, NOS																	X								
Islets, pancreatic	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+				M	M	M	+	+	M	+	M	+	M	M	M	M	M	M	M	M	M
Pituitary gland	+	+	+	+				+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																					X	X			X
Pars intermedia, adenoma																		X							
Thyroid gland	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+																								
Ovary	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma														X											
Hemangiosarcoma, metastatic												X													
Histiocytic sarcoma																X									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Uterus	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Histiocytic sarcoma																X									
Lymphoma malignant lymphocytic																									
Endometrium, polyp stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	3021	3061	3241	3251	3351	3161	3321	3331	3361	3401	3411	3031	3141	3191	3131	3431	3441	3591	3081	3101	3201	3231	3301	3461	3601	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic	X																									1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant undifferentiated cell type																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma	X	X							X		X															7
Hepatocellular adenoma							X	X	X									X								7
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant undifferentiated cell type																										1
Mesentery																										2
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant lymphocytic	X																									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic	X																									1
Papilloma squamous		X																		X	X					3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									1
Lymphoma malignant mixed																		X								1
CARDIOVASCULAR SYSTEM																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma							X																			1
Hemangiosarcoma, metastatic, ovary																										1
Lymphoma malignant lymphocytic	X																									1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma, NOS															X											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	+	+	M	+	M	M	+	+	14
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X	X						X		X	X		X			X	X	X	X		X	X		15
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma		X																								1
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic																										1
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic	X																									1
Endometrium, polyp stromal												X										X				2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	001	012	033	058	070	070	070	075	075	085	085	086	089	096	100	102	103	103	105	105	105	105	105	105	105
CARCASS ID	3581	3341	3531	3171	3501	3511	3521	3471	3261	3381	3071	3481	3391	3281	3571	3541	3491	3111	3041	3091	3151	3221	3271	3371	3451
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, ovary														X											
Hemangiosarcoma, metastatic, spleen																									
Lymphoma malignant lymphocytic																									
Lymph node	M	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type														X											
Axillary, lymphoma malignant undifferentiated cell type																									
Iliac, histiocytic sarcoma																X									
Iliac, lymphoma malignant histiocytic																									
Iliac, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant lymphocytic																									
Mediastinal, lymphoma malignant mixed																									
Mesenteric, lymphoma malignant histiocytic																									
Mesenteric, lymphoma malignant lymphocytic																						X			
Mesenteric, lymphoma malignant mixed																			X						
Mesenteric, lymphoma malignant undifferentiated cell type														X											
Mesenteric, osteosarcoma, metastatic, uncertain primary site															X										
Renal, lymphoma malignant histiocytic																									
Renal, lymphoma malignant lymphocytic																									
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	M	M	+	+				+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Hemangiosarcoma, metastatic, uterus																				X					
Histiocytic sarcoma																X									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed																			X						
Lymphoma malignant undifferentiated cell type														X											
Thymus	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	3021	3061	3241	3251	3351	3161	3321	3331	3361	3401	3411	3031	3141	3191	3311	3431	3441	3591	3081	3101	3201	3231	3301	3461	3601	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma, metastatic, ovary																										1
Hemangiosarcoma, metastatic, spleen																									X	1
Lymphoma malignant lymphocytic	X																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant undifferentiated cell type																										1
Axillary, lymphoma malignant undifferentiated cell type																	X									1
Iliac, histiocytic sarcoma																										1
Iliac, lymphoma malignant histiocytic			X																							1
Iliac, lymphoma malignant mixed					X													X						X		3
Mediastinal, lymphoma malignant histiocytic			X																							1
Mediastinal, lymphoma malignant lymphocytic	X																									1
Mediastinal, lymphoma mal mixed																								X		1
Mesenteric, lymphoma malignant histiocytic			X																							1
Mesenteric, lymphoma malignant lymphocytic	X																									2
Mesenteric, lymphoma malignant mixed				X	X							X						X						X		6
Mesenteric, lymphoma malignant undifferentiated cell type																	X									2
Mesenteric, osteosarcoma, metastatic, uncertain primary site																										1
Renal, lymphoma malignant histiocytic			X																							1
Renal, lymphoma mal lymphocytic	X																									1
Renal, lymphoma malignant mixed																								X		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant mixed				X	X													X						X		4
Lymphoma malignant undifferentiated cell type																	X									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																									X	2
Hemangiosarcoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant mixed				X	X							X						X						X		6
Lymphoma malignant undifferentiated cell type																	X									2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant mixed					X																					1
Lymphoma malignant undifferentiated cell type																	X									1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	001	012	033	058	070	070	070	075	075	085	085	086	089	096	100	102	103	103	105	105	105	105	105	105	105
CARCASS ID	3581	3341	3531	3171	3501	3511	3521	3471	3261	3381	3071	3481	3391	3281	3571	3541	3491	3111	3041	3091	3151	3221	3271	3371	3451
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Carcinoma																									
Skin	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma																	X								
Subcutaneous tissue, hemangioma															X										
Subcutaneous tissue, hemangiosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma									X		X														
Carcinoma, metastatic																						X			
Hepatocellular carcinoma, metastatic, liver										X															
Histiocytic sarcoma																X									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed																									
Osteosarcoma, metastatic, uncertain primary site															X										
Nose	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																		+	+			+			
Adenoma																			X						
Carcinoma																						X			
URINARY SYSTEM																									
Kidney	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																						X			
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type														X											
Osteosarcoma, metastatic, uncertain primary site															X										
Urinary bladder	+	+	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1,200 ppm (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL.
CARCASS ID	3021	3061	3241	3251	3351	3161	3321	3331	3361	3401	3411	3031	3141	3191	3311	3431	3441	3591	3081	3101	3201	3231	3301	3461	3601	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma squamous											X															1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, hemangiosarcoma																	X									1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic	X																									1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar adenoma							X	X									X									4
Alveolar/bronchiolar carcinoma																						X				3
Carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic, liver		X																								2
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									2
Lymphoma malignant mixed				X																						1
Osteosarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSES SYSTEM																										
Harderian gland																										3
Adenoma																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed				X	X													X								3
Lymphoma malignant undifferentiated cell type																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic			X																							1
Lymphoma malignant lymphocytic	X																									1
Lymphoma malignant mixed																		X								1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Liver: Hepatocellular Adenoma				
Overall Rates (a)	3/49 (6%)	7/50 (14%)	6/50 (12%)	7/47 (15%)
Adjusted Rates (b)	10.0%	19.7%	22.5%	20.0%
Terminal Rates (c)	3/30 (10%)	5/33 (15%)	5/24 (21%)	5/32 (16%)
Day of First Observation	729	683	509	520
Life Table Tests (d)	P=0.235	P=0.190	P=0.153	P=0.181
Logistic Regression Tests (d)	P=0.208	P=0.147	P=0.225	P=0.136
Cochran-Armitage Trend Test (d)	P=0.210			
Fisher Exact Test (d)		P=0.167	P=0.254	P=0.142
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	4/49 (8%)	2/50 (4%)	2/50 (4%)	7/47 (15%)
Adjusted Rates (b)	11.1%	5.0%	6.3%	19.4%
Terminal Rates (c)	2/30 (7%)	0/33 (0%)	1/24 (4%)	4/32 (13%)
Day of First Observation	631	477	578	589
Life Table Tests (d)	P=0.090	P=0.337N	P=0.407N	P=0.264
Logistic Regression Tests (d)	P=0.078	P=0.323N	P=0.328N	P=0.232
Cochran-Armitage Trend Test (d)	P=0.078			
Fisher Exact Test (d)		P=0.329N	P=0.329N	P=0.238
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	7/49 (14%)	9/50 (18%)	8/50 (16%)	13/47 (28%)
Adjusted Rates (b)	20.6%	23.7%	28.3%	34.5%
Terminal Rates (c)	5/30 (17%)	5/33 (15%)	6/24 (25%)	8/32 (25%)
Day of First Observation	631	477	509	520
Life Table Tests (d)	P=0.093	P=0.435	P=0.358	P=0.124
Logistic Regression Tests (d)	P=0.070	P=0.390	P=0.503	P=0.081
Cochran-Armitage Trend Test (d)	P=0.072			
Fisher Exact Test (d)		P=0.410	P=0.517	P=0.086
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	5/50 (10%)	0/50 (0%)	3/50 (6%)	4/47 (9%)
Adjusted Rates (b)	14.8%	0.0%	10.3%	11.7%
Terminal Rates (c)	3/30 (10%)	0/33 (0%)	1/24 (4%)	3/32 (9%)
Day of First Observation	681		702	598
Life Table Tests (d)	P=0.354	P=0.031N	P=0.477N	P=0.489N
Logistic Regression Tests (d)	P=0.335	P=0.036N	P=0.409N	P=0.545N
Cochran-Armitage Trend Test (d)	P=0.334			
Fisher Exact Test (d)		P=0.028N	P=0.357N	P=0.540N
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)	3/47 (6%)
Adjusted Rates (b)	0.0%	8.6%	4.2%	7.8%
Terminal Rates (c)	0/30 (0%)	2/33 (6%)	1/24 (4%)	1/32 (3%)
Day of First Observation		686	729	523
Life Table Tests (d)	P=0.228	P=0.134	P=0.455	P=0.118
Logistic Regression Tests (d)	P=0.210	P=0.114	P=0.455	P=0.114
Cochran-Armitage Trend Test (d)	P=0.211			
Fisher Exact Test (d)		P=0.121	P=0.500	P=0.110
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	5/50 (10%)	3/50 (6%)	4/50 (8%)	7/47 (15%)
Adjusted Rates (b)	14.8%	8.6%	14.2%	18.9%
Terminal Rates (c)	3/30 (10%)	2/33 (6%)	2/24 (8%)	4/32 (13%)
Day of First Observation	681	686	702	523
Life Table Tests (d)	P=0.182	P=0.331N	P=0.627N	P=0.386
Logistic Regression Tests (d)	P=0.156	P=0.375N	P=0.567N	P=0.330
Cochran-Armitage Trend Test (d)	P=0.157			
Fisher Exact Test (d)		P=0.357N	P=0.500N	P=0.336

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	12/49 (24%)	19/48 (40%)	21/49 (43%)	15/46 (33%)
Adjusted Rates (b)	36.9%	51.0%	58.0%	46.9%
Terminal Rates (c)	10/30 (33%)	15/33 (45%)	10/24 (42%)	15/32 (47%)
Day of First Observation	653	653	398	729
Life Table Tests (d)	P=0.410	P=0.146	P=0.014	P=0.382
Logistic Regression Tests (d)	P=0.344	P=0.066	P=0.033	P=0.278
Cochran-Armitage Trend Test (d)	P=0.367			
Fisher Exact Test (d)		P=0.084	P=0.043	P=0.258
Forestomach: Squamous Papilloma				
Overall Rates (e)	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/47 (6%)
Adjusted Rates (b)	10.0%	3.0%	4.2%	9.4%
Terminal Rates (c)	3/30 (10%)	1/33 (3%)	1/24 (4%)	3/32 (9%)
Day of First Observation	729	729	729	729
Life Table Tests (d)	P=0.439	P=0.271N	P=0.387N	P=0.634N
Logistic Regression Tests (d)	P=0.439	P=0.271N	P=0.387N	P=0.634N
Cochran-Armitage Trend Test (d)	P=0.418			
Fisher Exact Test (d)		P=0.309N	P=0.309N	P=0.631
Thyroid Gland: Follicular Cell Adenoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)	0/47 (0%)
Adjusted Rates (b)	0.0%	0.0%	12.0%	0.0%
Terminal Rates (c)	0/30 (0%)	0/33 (0%)	1/24 (4%)	0/32 (0%)
Day of First Observation			629	
Life Table Tests (d)	P=0.405	(f)	P=0.050	(f)
Logistic Regression Tests (d)	P=0.404	(f)	P=0.063	(f)
Cochran-Armitage Trend Test (d)	P=0.404			
Fisher Exact Test (d)		(f)	P=0.059	(f)
Thyroid Gland: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)	0/47 (0%)
Adjusted Rates (b)	3.3%	0.0%	12.0%	0.0%
Terminal Rates (c)	1/30 (3%)	0/33 (0%)	1/24 (4%)	0/32 (0%)
Day of First Observation	729		629	
Life Table Tests (d)	P=0.592	P=0.481N	P=0.140	P=0.487N
Logistic Regression Tests (d)	P=0.593	P=0.481N	P=0.178	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.594			
Fisher Exact Test (d)		P=0.500N	P=0.181	P=0.515N
Uterus: Stromal Polyp				
Overall Rates (e)	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/47 (4%)
Adjusted Rates (b)	10.0%	5.9%	3.8%	6.3%
Terminal Rates (c)	3/30 (10%)	1/33 (3%)	0/24 (0%)	2/32 (6%)
Day of First Observation	729	722	713	729
Life Table Tests (d)	P=0.422N	P=0.457N	P=0.393N	P=0.470N
Logistic Regression Tests (d)	P=0.429N	P=0.490N	P=0.369N	P=0.470N
Cochran-Armitage Trend Test (d)	P=0.435N			
Fisher Exact Test (d)		P=0.500N	P=0.309N	P=0.530N
Circulatory System: Hemangiosarcoma				
Overall Rates (e)	2/50 (4%)	2/50 (4%)	1/50 (2%)	6/47 (13%)
Adjusted Rates (b)	5.8%	6.1%	3.3%	17.0%
Terminal Rates (c)	1/30 (3%)	2/33 (6%)	0/24 (0%)	4/32 (13%)
Day of First Observation	681	729	708	598
Life Table Tests (d)	P=0.054	P=0.670N	P=0.569N	P=0.142
Logistic Regression Tests (d)	P=0.044	P=0.684	P=0.519N	P=0.112
Cochran-Armitage Trend Test (d)	P=0.043			
Fisher Exact Test (d)		P=0.691N	P=0.500N	P=0.115

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (e)	4/50 (8%)	3/50 (6%)	1/50 (2%)	8/47 (17%)
Adjusted Rates (b)	12.3%	9.1%	3.3%	22.2%
Terminal Rates (c)	3/30 (10%)	3/33 (9%)	0/24 (0%)	5/32 (16%)
Day of First Observation	681	729	708	598
Life Table Tests (d)	P=0.078	P=0.457N	P=0.251N	P=0.194
Logistic Regression Tests (d)	P=0.063	P=0.514N	P=0.208N	P=0.143
Cochran-Armitage Trend Test (d)	P=0.062			
Fisher Exact Test (d)		P=0.500N	P=0.181N	P=0.149
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (e)	22/50 (44%)	10/50 (20%)	17/50 (34%)	11/47 (23%)
Adjusted Rates (b)	60.5%	26.6%	45.9%	33.1%
Terminal Rates (c)	16/30 (53%)	6/33 (18%)	6/24 (25%)	10/32 (31%)
Day of First Observation	624	599	398	670
Life Table Tests (d)	P=0.147N	P=0.007N	P=0.473N	P=0.012N
Logistic Regression Tests (d)	P=0.138N	P=0.010N	P=0.227N	P=0.022N
Cochran-Armitage Trend Test (d)	P=0.142N			
Fisher Exact Test (d)		P=0.009N	P=0.206N	P=0.027N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the exposed and control groups.

TABLE D4a. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	8/46	1/46	9/46
Methyl methacrylate	12/49	0/49	12/49
Propylene	(b) 13/41	0/41	(b) 13/41
1,2-Epoxybutane	19/47	3/47	22/47
Dichloromethane	4/46	0/46	4/46
Ethylene oxide	4/48	1/48	5/48
Bromoethane	2/48	0/48	2/48
Tetrachloroethylene	2/45	5/45	7/45
TOTAL	(b) 64/370 (17.3%)	10/370 (2.7%)	(b) 74/370 (20.0%)
SD (c)	13.55%	4.04%	13.97%
Range (d)			
High	19/47	5/45	22/47
Low	2/48	0/49	2/48
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	(e) 244/1,528 (16.0%)	(f) 12/1,528 (0.8%)	(e,f) 256/1,528 (16.8%)
SD (c)	10.80%	1.42%	11.09%
Range (d)			
High	18/49	3/50	19/49
Low	0/48	0/50	0/48

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes 11 chromophobe adenomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes four chromophobe adenomas
(f) Includes three adenocarcinomas, NOS

TABLE D4b. HISTORICAL INCIDENCE OF INTERMEDIA PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas in Controls
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories	
Propylene oxide	0/46
Methyl methacrylate	1/49
Propylene	0/41
1,2-Epoxybutane	0/47
Dichloromethane	0/46
Ethylene oxide	0/48
Bromoethane	0/48
Tetrachloroethylene	0/45
TOTAL	1/370 (0.3%)
SD (b)	0.72%
Range (c)	
High	1/49
Low	0/48
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	3/1,528 (0.2%)
SD (b)	0.64%
Range (c)	
High	1/43
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; no malignant tumors have been observed.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls: Lymphoma	Incidence in Controls: Lymphoma or Leukemia
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories		
Propylene oxide	12/50	12/50
Methyl methacrylate	8/50	8/50
Propylene	16/50	16/50
1,2-Epoxybutane	13/50	13/50
Dichloromethane	7/50	7/50
Ethylene oxide	9/49	9/49
Bromoethane	11/50	11/50
Tetrachloroethylene	8/49	8/49
TOTAL	84/398 (21.1%)	84/398 (21.1%)
SD (b)	6.08%	6.08%
Range (c)		
High	16/50	16/50
Low	7/50	7/50
Overall Historical Incidence for Untreated Controls in NTP Studies		
TOTAL	523/1,689 (31.0%)	537/1,689 (31.8%)
SD (b)	12.73%	12.20%
Range (c)		
High	37/50	(d) 38/50
Low	5/50	6/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 29/50

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE

	Chamber Control	120 ppm	600 ppm	1,200 ppm
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	47
ALIMENTARY SYSTEM				
Esophagus	(49)	(50)	(50)	(47)
Infiltration cellular, lymphocytic		2 (4%)		
Inflammation, acute			1 (2%)	
Gallbladder	(49)	(49)	(50)	(45)
Hyperplasia, lymphoid	2 (4%)			
Infiltration cellular, lymphocytic	14 (29%)	18 (37%)	15 (30%)	16 (36%)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active			1 (2%)	1 (2%)
Intestine large	(50)	(50)	(50)	(47)
Anorectal junction, inflammation, acute	1 (2%)			
Anorectal junction, inflammation, chronic active			1 (2%)	
Anorectal junction, ulcer				1 (2%)
Anus, erosion				1 (2%)
Anus, inflammation, acute			1 (2%)	1 (2%)
Anus, inflammation, chronic active				1 (2%)
Anus, ulcer			1 (2%)	
Intestine large, cecum	(49)	(50)	(50)	(47)
Inflammation, acute	1 (2%)			
Intestine large, rectum	(50)	(50)	(50)	(45)
Inflammation, acute	1 (2%)		1 (2%)	1 (2%)
Intestine small, duodenum	(49)	(50)	(50)	(47)
Inflammation, chronic active			1 (2%)	
Intestine small, ileum	(49)	(50)	(50)	(47)
Amyloid deposition	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Intestine small, jejunum	(49)	(50)	(50)	(47)
Diverticulum				1 (2%)
Necrosis				1 (2%)
Liver	(49)	(50)	(50)	(47)
Basophilic focus	1 (2%)	3 (6%)		
Bile stasis				1 (2%)
Congestion				1 (2%)
Cyst		1 (2%)		
Fatty change	1 (2%)		1 (2%)	3 (6%)
Hematopoietic cell proliferation	23 (47%)	16 (32%)	30 (60%)	26 (55%)
Hyperplasia		1 (2%)		
Hyperplasia, lymphoid	2 (4%)	1 (2%)		
Infarct	1 (2%)			
Infiltration cellular, lymphocytic	23 (47%)	16 (32%)	15 (30%)	21 (45%)
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, chronic		1 (2%)		
Inflammation, chronic active				1 (2%)
Necrosis	7 (14%)	4 (8%)	4 (8%)	4 (9%)
Thrombus	1 (2%)			
Vacuolization cytoplasmic			1 (2%)	1 (2%)
Hepatocyte, hypertrophy	1 (2%)			
Median lobe, angiectasis		1 (2%)		
Serosa, inflammation, chronic			1 (2%)	1 (2%)
Mesentery	(5)	(2)	(4)	(2)
Inflammation, chronic			1 (25%)	
Fat, necrosis	1 (20%)		1 (25%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE *(Continued)*

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ALIMENTARY SYSTEM (Continued)				
Pancreas	(50)	(50)	(50)	(47)
Hyperplasia, lymphoid	4 (8%)	1 (2%)		
Infiltration cellular, lymphocytic	17 (34%)	28 (56%)	25 (50%)	26 (55%)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic active	1 (2%)			1 (2%)
Acinus, atrophy	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Duct, cyst	1 (2%)		1 (2%)	
Salivary glands	(50)	(50)	(50)	(46)
Atrophy		1 (2%)		
Hyperplasia, lymphoid	4 (8%)			
Infiltration cellular, lymphocytic	28 (56%)	37 (74%)	33 (66%)	32 (70%)
Stomach	(50)	(50)	(50)	(47)
Hyperplasia, squamous, focal			1 (2%)	
Stomach, forestomach	(50)	(49)	(50)	(47)
Angiectasis				1 (2%)
Erosion	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hyperkeratosis	2 (4%)			
Hyperplasia, squamous	2 (4%)	6 (12%)	4 (8%)	4 (9%)
Hyperplasia, squamous, focal	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Infiltration cellular, lymphocytic	5 (10%)	6 (12%)	8 (16%)	5 (11%)
Inflammation, acute	2 (4%)	2 (4%)	6 (12%)	7 (15%)
Inflammation, chronic				1 (2%)
Inflammation, chronic active		4 (8%)	3 (6%)	3 (6%)
Ulcer	1 (2%)	1 (2%)	4 (8%)	4 (9%)
Stomach, glandular	(49)	(50)	(50)	(47)
Edema			1 (2%)	
Erosion	2 (4%)	4 (8%)	4 (8%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)			
Infiltration cellular, lymphocytic	15 (31%)	18 (36%)	22 (44%)	23 (49%)
Inflammation, acute	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active			1 (2%)	
Metaplasia, squamous		1 (2%)		
Mineralization		1 (2%)	2 (4%)	2 (4%)
Ulcer	2 (4%)		2 (4%)	
Mucosa, dilatation	10 (20%)	6 (12%)	10 (20%)	14 (30%)
Tooth		(1)		
Pulp, inflammation, acute		1 (100%)		
CARDIOVASCULAR SYSTEM				
Blood vessel	(50)	(50)	(50)	(47)
Aorta, mineralization		1 (2%)		
Heart	(50)	(50)	(50)	(47)
Fibrosis, focal		1 (2%)		
Infiltration cellular, lymphocytic	10 (20%)	13 (26%)	20 (40%)	18 (38%)
Inflammation, acute			3 (6%)	
Inflammation, chronic	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Inflammation, chronic active	2 (4%)			
Mineralization	1 (2%)	1 (2%)		1 (2%)
Atrium, thrombus			1 (2%)	
Coronary artery, inflammation, acute		1 (2%)		
Coronary artery, inflammation, chronic		1 (2%)	1 (2%)	
Valve, thrombus	1 (2%)			
ENDOCRINE SYSTEM				
Adrenal gland	(49)	(50)	(50)	(47)
Capsule, inflammation, acute			1 (2%)	
Capsule, spindle cell, hyperplasia	49 (100%)	50 (100%)	49 (98%)	45 (96%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
ENDOCRINE SYSTEM *(Continued)*				
Adrenal gland, cortex	(49)	(50)	(50)	(47)
Congestion				1 (2%)
Cyst	1 (2%)			1 (2%)
Degeneration, fatty	1 (2%)	9 (18%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia	1 (2%)			
Hypertrophy	1 (2%)	2 (4%)	2 (4%)	4 (9%)
Hypertrophy, diffuse				1 (2%)
Necrosis			1 (2%)	
Pigmentation	35 (71%)	37 (74%)	45 (90%)	37 (79%)
Thrombus	1 (2%)		1 (2%)	
Spindle cell, hyperplasia				1 (2%)
Adrenal gland, medulla	(49)	(50)	(49)	(47)
Hyperplasia	1 (2%)		1 (2%)	
Necrosis			1 (2%)	
Islets, pancreatic	(50)	(49)	(50)	(47)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Pituitary gland	(49)	(48)	(49)	(46)
Pars distalis, angiectasis	2 (4%)		2 (4%)	
Pars distalis, cyst		3 (6%)	3 (6%)	
Pars distalis, hemorrhage			1 (2%)	
Pars distalis, hyperplasia	12 (24%)	18 (38%)	14 (29%)	15 (33%)
Thyroid gland	(50)	(50)	(50)	(47)
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, lymphocytic	5 (10%)	6 (12%)	8 (16%)	6 (13%)
Inflammation, acute		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active		1 (2%)		3 (6%)
C-cell, hyperplasia			1 (2%)	
Follicle, dilatation	8 (16%)	5 (10%)	4 (8%)	5 (11%)
Follicle, hyperplasia	9 (18%)	13 (26%)	7 (14%)	10 (21%)
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Clitoral gland	(1)	(1)	(1)	(1)
Abscess	1 (100%)			
Cyst			1 (100%)	
Ovary	(50)	(49)	(50)	(47)
Abscess			2 (4%)	
Hemorrhage			1 (2%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)			
Hyperplasia, adenomatous				1 (2%)
Infiltration cellular, lymphocytic			1 (2%)	
Inflammation, acute			2 (4%)	4 (9%)
Mineralization				1 (2%)
Pigmentation, cholesterol, hemosiderin			1 (2%)	
Follicle, cyst			1 (2%)	
Follicle, cyst multilocular			1 (2%)	
Periovarian tissue, cyst	11 (22%)	8 (16%)	8 (16%)	7 (15%)
Oviduct			(1)	
Inflammation, acute			1 (100%)	
Uterus	(50)	(50)	(50)	(47)
Angiectasis	1 (2%)	2 (4%)		1 (2%)
Endometrium, hyperplasia, cystic	45 (90%)	43 (86%)	38 (76%)	38 (81%)
Endometrium, inflammation, acute	4 (8%)	1 (2%)	7 (14%)	6 (13%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
HEMATOPOIETIC SYSTEM				
Bone marrow	(50)	(50)	(50)	(47)
Angiectasis	1 (2%)			
Fibrosis	25 (50%)	32 (64%)	26 (52%)	21 (45%)
Fibrous osteodystrophy				4 (9%)
Myeloid cell, hyperplasia	33 (66%)	35 (70%)	38 (76%)	34 (72%)
Lymph node	(48)	(49)	(50)	(46)
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	2 (4%)	2 (4%)	
Inflammation, acute	1 (2%)			
Axillary, hyperplasia, lymphoid				1 (2%)
Bronchial, hyperplasia, lymphoid			1 (2%)	
Iliac, hyperplasia, lymphoid	3 (6%)			2 (4%)
Iliac, inflammation, acute				1 (2%)
Mediastinal, congestion				2 (4%)
Mediastinal, hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	5 (11%)
Mediastinal, inflammation, acute			1 (2%)	
Mesenteric, angiectasis	1 (2%)			1 (2%)
Mesenteric, congestion		5 (10%)	6 (12%)	7 (15%)
Mesenteric, hemorrhage				1 (2%)
Mesenteric, hyperplasia, lymphoid	26 (54%)	17 (35%)	21 (42%)	24 (52%)
Mesenteric, inflammation, acute	1 (2%)	2 (4%)	7 (14%)	7 (15%)
Renal, congestion			1 (2%)	
Renal, hyperplasia, lymphoid	2 (4%)		1 (2%)	1 (2%)
Renal, inflammation, acute			1 (2%)	1 (2%)
Lymph node, mandibular	(47)	(48)	(50)	(43)
Congestion				1 (2%)
Hyperplasia		1 (2%)	1 (2%)	
Hyperplasia, glandular			1 (2%)	
Hyperplasia, lymphoid	31 (66%)	29 (60%)	32 (64%)	25 (58%)
Inflammation, acute		2 (4%)	2 (4%)	1 (2%)
Pigmentation		1 (2%)	1 (2%)	
Spleen	(50)	(50)	(49)	(47)
Angiectasis				1 (2%)
Hematopoietic cell proliferation	41 (82%)	39 (78%)	41 (84%)	45 (96%)
Hyperplasia, lymphoid	16 (32%)	16 (32%)	13 (27%)	14 (30%)
Infiltration cellular			1 (2%)	
Inflammation, chronic	1 (2%)			
Necrosis	1 (2%)			
Pigmentation	37 (74%)	33 (66%)	34 (69%)	28 (60%)
Capsule, inflammation, acute			1 (2%)	
Thymus	(46)	(48)	(48)	(47)
Congestion		1 (2%)		1 (2%)
Cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Ectopic thyroid			1 (2%)	
Edema			1 (2%)	
Hyperplasia, lymphoid	7 (15%)	6 (13%)	10 (21%)	10 (21%)
INTEGUMENTARY SYSTEM				
Mammary gland	(49)	(50)	(48)	(46)
Ectasia	16 (33%)	18 (36%)	18 (38%)	11 (24%)
Inflammation, acute		1 (2%)		
Acinus, ectasia			1 (2%)	
Skin	(50)	(50)	(50)	(47)
Alopecia	9 (18%)	9 (18%)	8 (16%)	2 (4%)
Inflammation, acute	1 (2%)			
Inflammation, chronic			1 (2%)	
Ulcer	1 (2%)			
Back, ulcer		1 (2%)		
Foot, ulcer			1 (2%)	
Head, ulcer	1 (2%)		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
INTEGUMENTARY SYSTEM				
Skin (Continued)	(50)	(50)	(50)	(47)
Inguinal, inflammation, acute	1 (2%)			
Inguinal, ulcer			1 (2%)	
Subcutaneous tissue, edema			1 (2%)	1 (2%)
Subcutaneous tissue, hemorrhage	1 (2%)	1 (2%)		
Subcutaneous tissue, inflammation, acute			1 (2%)	1 (2%)
Ventral, inflammation, chronic	1 (2%)			
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(49)	(50)	(47)
Cranium, fracture				1 (2%)
Cranium, inflammation, chronic active				1 (2%)
Femur, fracture		1 (2%)	1 (2%)	1 (2%)
Skeletal muscle		(1)	(2)	
Head, inflammation, acute			2 (100%)	
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(47)
Compression			3 (6%)	1 (2%)
Hemorrhage	5 (10%)		4 (8%)	2 (4%)
Infiltration cellular, lymphocytic	4 (8%)	3 (6%)	4 (8%)	3 (6%)
Mineralization	35 (70%)	31 (62%)	30 (60%)	28 (60%)
Hippocampus, cyst				1 (2%)
Meninges, inflammation, acute		1 (2%)		1 (2%)
Nerve, inflammation, acute			1 (2%)	
Ventricle, dilatation	1 (2%)			
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(47)
Congestion	13 (26%)	2 (4%)	9 (18%)	8 (17%)
Hemorrhage	5 (10%)	8 (16%)	7 (14%)	6 (13%)
Hyperplasia, lymphoid	5 (10%)	1 (2%)		
Infiltration cellular, lymphocytic	30 (60%)	42 (84%)	40 (80%)	43 (91%)
Mineralization	2 (4%)	7 (14%)		1 (2%)
Pigmentation, cholesterol	1 (2%)			
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)	3 (6%)	4 (9%)
Alveolus, infiltration cellular, histiocytic	2 (4%)	2 (4%)	3 (6%)	7 (15%)
Interstitium, inflammation, acute	3 (6%)		1 (2%)	1 (2%)
Interstitium, inflammation, chronic		1 (2%)	1 (2%)	
Peribronchiolar, inflammation, acute	1 (2%)		1 (2%)	
Pleura, inflammation, chronic			1 (2%)	1 (2%)
Pleura, interstitium, inflammation, acute			1 (2%)	
Nose	(50)	(50)	(50)	(47)
Lumen, hemorrhage	31 (62%)	28 (56%)	28 (56%)	25 (53%)
Mucosa, inflammation, acute	3 (6%)	1 (2%)	4 (8%)	6 (13%)
Nasolacrimal duct, hemorrhage	1 (2%)	1 (2%)	1 (2%)	
Nasolacrimal duct, inflammation, acute		1 (2%)	5 (10%)	2 (4%)
Olfactory epithelium, degeneration	48 (96%)	31 (62%)	41 (82%)	31 (66%)
Olfactory epithelium, inflammation, acute		1 (2%)		3 (6%)
Olfactory epithelium, metaplasia				3 (6%)
Respiratory epithelium, degeneration	18 (36%)	19 (38%)	14 (28%)	12 (26%)
Respiratory epithelium, inflammation, acute				2 (4%)
Turbinate, inflammation, acute	1 (2%)	1 (2%)	1 (2%)	
Vomeronasal organ, inflammation, acute	1 (2%)			

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF TOLUENE (Continued)

	Chamber Control	120 ppm	600 ppm	1,200 ppm
RESPIRATORY SYSTEM (Continued)				
Trachea	(50)	(50)	(50)	(47)
Hemorrhage				1 (2%)
Inflammation, acute			1 (2%)	
Glands, inflammation, acute				1 (2%)
Lumen, hemorrhage				1 (2%)
SPECIAL SENSES SYSTEM				
Eye		(1)		
Atrophy		1 (100%)		
Harderian gland		(3)	(2)	(3)
Hyperplasia				1 (33%)
Infiltration cellular, lymphocytic		1 (33%)		
Inflammation, acute				1 (33%)
Inflammation, chronic active				1 (33%)
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(47)
Abscess		1 (2%)	1 (2%)	
Congestion				1 (2%)
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	6 (12%)	1 (2%)		
Infarct	1 (2%)			1 (2%)
Infiltration cellular, lymphocytic	31 (62%)	42 (84%)	36 (72%)	38 (81%)
Inflammation			1 (2%)	
Inflammation, acute				1 (2%)
Inflammation, chronic			1 (2%)	
Metaplasia, osseous	4 (8%)	1 (2%)	3 (6%)	4 (9%)
Mineralization		1 (2%)		
Regeneration				1 (2%)
Capsule, inflammation, chronic			1 (2%)	
Pelvis, dilatation	2 (4%)	1 (2%)	1 (2%)	
Pelvis, inflammation, acute			2 (4%)	
Renal tubule, casts protein	6 (12%)	11 (22%)	5 (10%)	12 (26%)
Renal tubule, dilatation	24 (48%)	16 (32%)	30 (60%)	24 (51%)
Renal tubule, necrosis	5 (10%)	7 (14%)	9 (18%)	6 (13%)
Renal tubule, pigmentation		1 (2%)	1 (2%)	1 (2%)
Renal tubule, regeneration	14 (28%)	13 (26%)	23 (46%)	15 (32%)
Ureter		(1)	(1)	
Dilatation		1 (100%)	1 (100%)	
Infiltration cellular, lymphocytic		1 (100%)		
Urinary bladder	(50)	(50)	(50)	(47)
Angiectasis	1 (2%)			1 (2%)
Ectasia			2 (4%)	
Hyperplasia, lymphoid	5 (10%)	1 (2%)		
Infiltration cellular, lymphocytic	31 (62%)	39 (78%)	34 (68%)	35 (74%)

APPENDIX E

RESULTS OF SEROLOGIC ANALYSIS

APPENDIX E. RESULTS OF SEROLOGIC ANALYSIS

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results.

Data were collected on 5 F344/N control rats of each sex and 10 female $B6C3F_1$ control mice killed at 15 months and from 5/50 or 5/60 randomly selected control animals of each sex and species that lived to the end of the studies. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) (15 mo) Reo 3 (reovirus type 3) (15 mo) GDVII (Theiler's encephalomyelitis virus) (15 mo) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) (15 mo) Sendai (15 mo)	M. Ad (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) (15 mo) **IFA** EDIM (epizootic diarrhea of infant mice) (24 mo)	MHV (mouse hepatitis virus) Reo 3 (24 mo) M. Ad. (24 mo) PVM (24 mo) Sendai (24 mo) Ectro (24 mo) GDVII (24 mo) *M. pul. (Mycoplasma pulmonis)* (24 mo) *M. arth. (Mycoplasma arthritidis)* (24 mo)
Rats	PVM (15 mo) KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (15 mo)		RCV/SDA (rat coronavirus/sialodacryoadenitis) (15,24 mo) Sendai (24 mo) PVM (24 mo) *M. pul.* (24 mo) *M. arth.* (24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE FIFTEEN-MONTH AND TWO-YEAR INHALATION STUDIES OF TOLUENE (a)

	Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS			
	15	9/10	Sendai
		3/10	RCV/SDA
	24	10/10	PVM
		10/10	Sendai
		2/10	RCV/SDA
		1/10	Possibly *M. arth.*
		2/10	*M. pul.* (b)
MICE			
	15	8/10	MHV
	24	9/10	PVM
		9/9	MHV
		3/7	EDIM

(a) Blood samples were taken at 15 and 24 months from control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX F

INGREDIENTS, NUTRIENT COMPOSITION, AND

CONTAMINANT LEVELS IN

NIH 07 RAT AND MOUSE RATION

Pelleted Diet: October 1982 to November 1984

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

TABLE F1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.01 ± 1.07	21.3-26.3	26
Crude fat (percent by weight)	5.25 ± 0.70	3.3-6.5	26
Crude fiber (percent by weight)	3.51 ± 0.51	2.8-5.6	26
Ash (percent by weight)	6.66 ± 0.32	6.1-7.1	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,289 ± 4,640	4,100-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	18.42 ± 4.01	12.0-27.0	26
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.27 ± 0.13	0.95-1.54	26
Phosphorus (percent)	0.97 ± 0.06	0.87-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.54 ± 0.17	0.17-0.77	26
Cadmium (ppm)	<0.10		26
Lead (ppm)	0.58 ± 0.20	0.33-1.27	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.32 ± 0.07	0.13-0.42	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	9.96 ± 4.90	0.10-22.0	26
Nitrite nitrogen (ppm) (b)	1.05 ± 1.61	0.10-7.20	26
BHA (ppm) (c)	3.23 ± 3.95	2.00-17.00	26
BHT (ppm) (c)	2.62 ± 2.40	1.00-12.00	26
Aerobic plate count (CFU/g) (d)	47,473 ± 37,556	7,100-130,000	26
Coliform (MPN/g) (e)	40.69 ± 97.61	3.00-460	26
E. coli (MPN/g)	3.04 ± 0.20	3.00-4.00	26
Total nitrosamines (ppb) (f)	5.64 ± 5.66	1.80-30.90	26
N-Nitrosodimethylamine (ppb) (f)	4.59 ± 5.67	0.80-30.00	26
N-Nitrosopyrrolidine (ppb) (f)	1.05 ± 0.24	0.90-1.70	26
Pesticides (ppm)			
α-BHC (a,g)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (a)	<0.05		26
Dieldrin (a)	<0.01		26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (h)	0.11 ± 0.09	0.05-0.45	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		26
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Fifteen lots contained more than 0.05 ppm.

APPENDIX G

METHODS FOR EVALUATION OF REPRODUCTIVE ORGAN TOXICITY IN THE FOURTEEN-WEEK AND FIFTEEN-WEEK INHALATION STUDIES OF TOLUENE

APPENDIX G. METHODS

The right testis and epididymis of rats and mice were removed and placed in a disposable weigh boat. The epididymis was dissected free of the testis, and excess fat was trimmed away.

The right cauda epididymis was removed, weighed, and placed in a prewarmed (32° C) Petri dish containing 1 ml sterile prewarmed (32° C) Tyrode's solution (mice) or sterile phosphate-buffered saline (rats).

The right cauda was secured with a small forceps, gently chopped with a scalpel, and incubated for 15 minutes (mice) or 5 minutes (rats) to release its contents. The right testis and corpus epididymis were weighed. Immediately before the end of the incubation period, a prewarmed (32° C) standard microscope slide and an American Optical hemocytometer were placed on a microscope for the evaluation of sperm motility and sperm progressive drive range. When the incubation period was completed, the suspension was mixed by gently swirling the Petri dish and was aspirated with a prewarmed (32° C) Pasteur pipet. The same pipet was used to distribute samples for the motility and drive range determinations. Two drops of suspension were placed on the microscope slide and covered with a prewarmed (32° C) coverslip (24 × 50 mm). One drop of suspension was used to fill the hemocytometer. Only the assays for progressive motility and general motility required live samples. Each sample was evaluated by two viewers, A and B, working independently.

Using the 40× objective of a microscope, Viewer A randomly selected motile sperm. The time required for each randomly selected sperm to traverse 0.1 mm (two small squares) was noted to the nearest 100th second with a stopwatch. Only sperm moving horizontally or vertically in a straight line were considered. If no progressive motility or fewer than 50 motile sperm were observed, a statement to that effect was entered on the data form. All data recorded for this test were entered by a designated recorder. Viewer A observed and timed the progressive motility of 25 sperm cells.

Viewer B, also using the 40× objective of a microscope, initially determined whether more or less than 50% of the sperm in the viewing field were motile. Viewer B then counted in increments of 5% the percentage of sperm above or below 50% of the sperm that were motile. On completion of the motility estimations for the field, Viewer B recorded the findings on the data sheet. Viewer B determined motility for five separate fields of view. Viewers A and B then changed workstations, and the measurements were repeated.

After the live sperm tests were completed, a sperm count was performed. The Petri dish containing the sperm was gently swirled to resuspend the cells. A 1-ml glass micropipet then was used to pipet 0.5 ml of the sperm suspension into a glass test tube (15 × 150 mm) containing 2 ml sterile Tyrode's solution (mice) or 4 ml sterile phosphate-buffered saline (rats). After being agitated with a vortex mixer, the suspension was immersed in a hot water bath for about 1 minute. The sperm mixture then was aspirated with a Pasteur pipet, and a drop was placed in the counting chamber of a hemocytometer. The sperm in five large grid areas were counted, and the results, as well as the initial dilution factor, were recorded on the data form. Two counts were performed, each with a separately aspirated sample.

The suspension remaining in the Petri dish was pipetted with a Pasteur pipet into a disposable culture tube (10 × 75 mm) containing 1 drop of eosin Y stain (1%) in water and allowed to stand for 45 minutes. At the conclusion of the staining time, the solution was gently aspirated. One drop of the stained suspension was placed on a standard, pencil-labeled microscope slide and was spread by one pass of a coverslip. Six smears were prepared from each suspension. The slides were placed at an angle in a microscope slide box and covered with transparent polyethylene. After drying, the slides were coverslipped.

Smears for evaluation of the vaginal cytology were taken between 7:00 a.m. and 9:00 a.m. from 7-9 (mice) or 12-14 (rats) consecutive days before the animals were killed and also on the morning of the kill. The methods used for taking smears were as described in the protocol provided by the laboratory evaluating sperm morphology and vaginal cytology.

The microscope slides used for making the smears were marked into a grid consisting of seven squares on the back of the slide. The squares were labeled 1 through 7. Since more smears than the seven called for in the original protocol were made, a second slide was prepared for each animal with squares labeled 8 through the last day a smear was taken for that animal. Slides were prepared in duplicate for each animal.

One drop of 0.9% saline solution was placed on the appropriate square of the microscope slide. A medicine dropper was then moistened by aspirating the saline solution. The tip of the moistened medicine dropper was placed in the vagina, and the vaginal fluids were aspirated several times. The contents of the medicine dropper were transferred onto the microscope slide and allowed to air dry. The slides were stored in closed slide boxes between collection days.

After completion of smearing, the slides were loaded into glass racks and were stained as follows:

1. Absolute ethanol - 1 minute
2. 95% ethanol - 1 minute
3. 95% ethanol - 1 minute
4. Distilled water - 1 minute
5. 0.5% toluidine blue in 20% ethanol - 45 seconds or less
6. Running tap water - until tap water ran clear
7. Distilled water - 1 minute

The stained slides were blotted gently with bibulous paper; care was taken not to use the same paper on more than one slide. The slides were allowed to dry completely and then were coverslipped.

The slides for both the vaginal cytology and sperm morphology evaluations were identified by a coding system, as described in the protocol, and were shipped to the laboratory evaluating sperm morphology and vaginal cytology.

APPENDIX H

HEMATOLOGIC AND SERUM CHEMICAL DATA IN THE THIRTEEN-WEEK GAVAGE AND FOURTEEN-WEEK AND FIFTEEN-WEEK INHALATION STUDIES AND HEMATOLOGIC DATA AND ORGAN WEIGHTS IN THE FIFTEEN-MONTH INHALATION STUDIES OF RATS AND MICE EXPOSED TO TOLUENE

TABLE H1. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE (a)

Analysis	Vehicle Control	312 mg/kg	625 mg/kg	1,250 mg/kg	2,500 mg/kg
MALE					
Number examined (b)	10	10	10	10	2
Eosinophils ($10^3/mm^3$)	0.04 ± 0.013	0.09 ± 0.021	0.06 ± 0.025	0.05 ± 0.017	(c)
Hematocrit (percent)	42.3 ± 0.32	43.3 ± 0.62	42.9 ± 0.45	43.1 ± 0.47	43.2 ± 2.10
Hemoglobin (g/dl)	16.2 ± 0.13	16.7 ± 0.26	16.5 ± 0.16	16.5 ± 0.24	16.7 ± 0.95
Lymphocytes ($10^3/mm^3$)	4.5 ± 0.20	4.3 ± 0.36	5.3 ± 0.23	4.5 ± 0.27	(c)
Mean corpuscular hemoglobin (pg)	20.5 ± 0.08	20.4 ± 0.09	**20.0 ± 0.11	**20.0 ± 0.14	21.3 ± 0.70
Mean corpuscular hemoglobin concentration (g/dl)	38.4 ± 0.17	38.5 ± 0.12	38.2 ± 0.08	38.4 ± 0.24	38.6 ± 0.35
Mean cell volume (μ^3)	53.3 ± 0.15	53.0 ± 0.21	**52.2 ± 0.25	**52.2 ± 0.13	55.5 ± 1.50
Methemoglobin (percent)	2.26 ± 0.722	2.84 ± 0.595	3.83 ± 0.863	3.17 ± 0.934	1.54 ± 1.537
Monocytes ($10^3/mm^3$)	0.13 ± 0.039	0.09 ± 0.020	0.18 ± 0.029	0.13 ± 0.032	(c)
Platelets ($10^3/mm^3$)	583 ± 8.3	575 ± 10.8	591 ± 17.0	**640 ± 11.9	*685 ± 35.0
Erythrocytes ($10^6/mm^3$)	7.94 ± 0.060	*8.17 ± 0.111	**8.25 ± 0.064	**8.27 ± 0.092	7.82 ± 0.190
Reticulocytes (percent)	2.74 ± 0.167	3.18 ± 0.294	*3.40 ± 0.204	**3.57 ± 0.194	*3.95 ± 0.350
Segmented neutrophils ($10^3/mm^3$)	1.13 ± 0.074	1.27 ± 0.079	1.30 ± 0.143	1.17 ± 0.089	(c)
Leukocytes ($10^3/mm^3$)	5.82 ± 0.265	5.70 ± 0.374	6.86 ± 0.283	5.93 ± 0.325	6.70 ± 0.800
Albumin (g/dl)	3.7 ± 0.05	3.8 ± 0.07	3.8 ± 0.07	**4.0 ± 0.05	4.1 ± 0.30
Blood urea nitrogen (mg/dl)	10.6 ± 0.27	10.6 ± 0.48	11.3 ± 0.31	11.4 ± 0.69	12.5 ± 1.60
Calcium (g/dl)	11.0 ± 0.05	11.0 ± 0.14	*11.3 ± 0.08	**11.4 ± 0.09	10.9 ± 0.30
Lactic dehydrogenase (IU/liter)	423 ± 48.8	433 ± 45.5	478 ± 56.0	478 ± 59.2	488 ± 79.0
Inorganic phosphorus (mg/dl)	6.74 ± 0.114	7.08 ± 0.230	7.04 ± 0.106	**7.69 ± 0.188	*7.70 ± 0.500
Total protein (g/dl)	6.96 ± 0.156	7.09 ± 0.186	7.14 ± 0.169	*7.55 ± 0.195	7.85 ± 0.450
FEMALE					
Number examined (b)	10	10	10	10	9
Eosinophils ($10^3/mm^3$)	0.07 ± 0.025	0.05 ± 0.022	0.04 ± 0.011	0.08 ± 0.017	(c)
Hematocrit (percent)	41.6 ± 0.52	42.6 ± 0.27	41.7 ± 0.54	42.2 ± 0.59	40.8 ± 0.43
Hemoglobin (g/dl)	15.8 ± 0.22	16.1 ± 0.08	15.8 ± 0.19	16.1 ± 0.23	15.4 ± 0.20
Lymphocytes ($10^3/mm^3$)	4.1 ± 0.36	4.3 ± 0.34	3.6 ± 0.10	4.4 ± 0.18	(c)
Mean corpuscular hemoglobin (pg)	21.7 ± 0.08	21.5 ± 0.06	21.4 ± 0.12	*21.4 ± 0.09	21.5 ± 0.10
Mean corpuscular hemoglobin concentration (g/dl)	37.9 ± 0.13	37.7 ± 0.15	37.9 ± 0.21	38.1 ± 0.13	37.7 ± 0.18
Mean cell volume (μ^3)	57.5 ± 0.17	56.9 ± 0.23	**56.4 ± 0.31	**56.1 ± 0.28	**56.9 ± 0.11
Methemoglobin (percent)	3.04 ± 0.768	2.31 ± 0.589	2.90 ± 0.713	3.20 ± 0.674	2.20 ± 0.697
Monocytes ($10^3/mm^3$)	0.04 ± 0.017	0.05 ± 0.022	*0.10 ± 0.012	*0.12 ± 0.030	(c)
Platelets ($10^3/mm^3$)	592 ± 20.5	597 ± 13.7	602 ± 14.1	622 ± 7.1	*654 ± 24.9
Erythrocytes ($10^6/mm^3$)	7.27 ± 0.086	7.48 ± 0.045	7.37 ± 0.084	7.52 ± 0.123	7.16 ± 0.068
Reticulocytes (percent)	2.92 ± 0.223	2.97 ± 0.162	2.75 ± 0.312	3.02 ± 0.372	**4.57 ± 0.356
Segmented neutrophils ($10^3/mm^3$)	1.09 ± 0.089	0.83 ± 0.093	0.81 ± 0.079	1.01 ± 0.125	(d) 1.28 ± 0.219
Leukocytes ($10^3/mm^3$)	5.29 ± 0.353	5.21 ± 0.292	4.57 ± 0.148	5.61 ± 0.290	(d) 6.70 ± 0.800
Albumin (g/dl)	3.6 ± 0.07	3.7 ± 0.07	3.7 ± 0.05	*3.8 ± 0.05	*3.8 ± 0.07
Blood urea nitrogen (mg/dl)	10.5 ± 0.36	11.8 ± 0.48	10.9 ± 0.13	11.5 ± 0.49	10.2 ± 0.57
Calcium (g/dl)	10.7 ± 0.12	10.7 ± 0.09	10.7 ± 0.08	10.8 ± 0.06	*10.9 ± 0.14
Lactic dehydrogenase (IU/liter)	351 ± 41.6	368 ± 36.5	406 ± 65.8	392 ± 39.0	390 ± 32.5
Inorganic phosphorus (mg/dl)	6.08 ± 0.238	6.00 ± 0.203	6.33 ± 0.259	6.43 ± 0.168	**7.30 ± 0.216
Total protein (g/dl)	6.53 ± 0.183	6.76 ± 0.208	6.80 ± 0.113	**7.14 ± 0.136	*7.06 ± 0.187

(a) Mean ± standard error. P values are vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977). IU = international units.
(b) Except as noted
(c) Fewer than two animals were examined.
(d) Two animals were examined.
*P<0.05
**P<0.01

TABLE H2. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR RATS IN THE FIFTEEN-WEEK INHALATION STUDIES OF TOLUENE (a)

Analysis	Control	100 ppm	625 ppm	1,250 ppm	2,500 ppm	3,000 ppm
MALE						
Number examined	10	10	10	10	10	2
Leukocytes (10^3/mm^3)	8.19 ± 0.441	8.12 ± 0.409	7.43 ± 0.367	7.19 ± 0.443	7.86 ± 0.623	7.70 ± 0.095
Lymphocytes (percent)	77.5 ± 1.86	73.7 ± 1.31	73.7 ± 2.13	73.2 ± 3.01	*71.1 ± 2.12	71.5 ± 3.50
Segmented neutrophils (percent)	19.2 ± 1.91	23.1 ± 1.52	22.2 ± 2.22	23.8 ± 2.75	24.5 ± 2.22	24.0 ± 2.00
Monocytes (percent)	2.7 ± 0.30	1.9 ± 0.31	2.6 ± 0.58	1.8 ± 0.47	3.1 ± 0.53	3.5 ± 1.50
Eosinophils (percent)	0.6 ± 0.27	1.3 ± 0.30	1.4 ± 0.27	1.2 ± 0.25	1.1 ± 0.23	1.0 ± 0.00
Hematocrit (percent)	50.3 ± 1.17	51.8 ± 0.51	51.1 ± 0.65	51.0 ± 0.96	50.6 ± 1.17	48.3 ± 2.05
Hemoglobin (g/dl)	17.3 ± 0.47	17.9 ± 0.19	17.6 ± 0.15	17.4 ± 0.24	17.3 ± 0.55	17.0 ± 0.10
Mean corpuscular hemoglobin (pg)	21.3 ± 0.21	21.3 ± 0.12	21.1 ± 0.17	20.8 ± 0.16	21.0 ± 0.28	22.1 ± 0.10
Mean corpuscular hemoglobin concentration (g/dl)	34.4 ± 0.45	34.6 ± 0.40	34.4 ± 0.60	34.2 ± 0.47	34.1 ± 0.67	35.3 ± 1.30
Mean cell volume (cubic microns)	61.8 ± 0.73	61.7 ± 0.52	61.2 ± 0.73	60.9 ± 0.69	61.6 ± 0.56	63.0 ± 2.00
Methemoglobin (g/dl)	1.19 ± 0.263	1.35 ± 0.221	1.28 ± 0.204	1.58 ± 0.333	0.91 ± 0.270	1.12 ± 0.649
Platelets (10^3/mm^3)	555 ± 29.0	542 ± 18.5	520 ± 13.9	547 ± 11.8	548 ± 20.1	564 ± 27.0
Erythrocytes (10^6/mm^3)	8.13 ± 0.199	8.39 ± 0.086	8.35 ± 0.065	8.36 ± 0.094	8.22 ± 0.196	7.70 ± 0.095
Reticulocytes (10^6/mm^3)	3.22 ± 0.286	3.18 ± 0.252	3.18 ± 0.364	2.86 ± 0.367	3.38 ± 0.256	4.10 ± 0.000
Albumin/globulin ratio	1.03 ± 0.021	1.04 ± 0.022	1.06 ± 0.016	1.05 ± 0.027	**1.12 ± 0.020	*1.15 ± 0.050
Albumin (g/dl)	3.75 ± 0.040	3.77 ± 0.047	3.70 ± 0.015	3.69 ± 0.046	3.83 ± 0.063	3.75 ± 0.050
Urea nitrogen (mg/dl)	18.5 ± 0.68	18.7 ± 1.03	18.6 ± 0.64	18.3 ± 0.92	17.1 ± 0.78	19.6 ± 0.20
Calcium (mg/dl)	11.0 ± 0.17	11.1 ± 0.18	10.8 ± 0.09	11.0 ± 0.14	11.1 ± 0.16	11.0 ± 0.20
Chloride (meq/liter)	106 ± 1.1	105 ± 1.1	104 ± 1.1	104 ± 1.2	104 ± 1.1	109 ± 6.5
Cholinesterase (IU/liter)	714 ± 16	712 ± 18	682 ± 15	671 ± 14	**630 ± 19	*595 ± 9
Creatinine (mg/dl)	0.54 ± 0.043	0.61 ± 0.038	0.50 ± 0.021	0.48 ± 0.025	0.51 ± 0.035	0.45 ± 0.050
GGT (IU/liter)	1.1 ± 0.10	1.1 ± 0.10	1.2 ± 0.13	1.0 ± 0.00	1.3 ± 0.15	1.5 ± 0.50
Inorganic phosphorus (mg/dl)	7.12 ± 0.213	7.01 ± 0.333	6.39 ± 0.133	6.97 ± 0.294	7.46 ± 0.501	7.35 ± 0.050
Potassium (meq/liter)	5.75 ± 0.174	5.75 ± 0.201	5.36 ± 0.136	5.75 ± 0.190	6.29 ± 0.192	6.45 ± 0.650
Glucose (mg/dl)	144 ± 5.8	147 ± 5.2	148 ± 4.0	148 ± 3.5	144 ± 4.4	138 ± 0.0
Sodium (meq/liter)	147 ± 1.1	147 ± 1.2	147 ± 0.7	146 ± 1.2	148 ± 1.4	152 ± 7.0
Total bilirubin (mg/dl)	0.26 ± 0.027	0.22 ± 0.013	0.27 ± 0.033	0.26 ± 0.037	0.25 ± 0.022	0.15 ± 0.050
Total protein (g/dl)	7.42 ± 0.088	7.45 ± 0.073	7.24 ± 0.045	7.25 ± 0.109	7.31 ± 0.167	7.05 ± 0.150
FEMALE						
Number examined (b)	10	10	10	10	10	10
Leukocytes (10^3/mm^3)	7.26 ± 0.392	6.75 ± 0.387	6.46 ± 0.480	*5.98 ± 0.352	**5.64 ± 0.342	*6.39 ± 0.385
Lymphocytes (percent)	76.9 ± 1.91	72.2 ± 2.39	74.8 ± 1.82	77.0 ± 1.98	76.3 ± 1.80	77.5 ± 1.76
Segmented neutrophils (percent)	20.4 ± 1.79	24.7 ± 2.25	21.9 ± 1.46	19.7 ± 2.04	21.4 ± 1.83	19.2 ± 1.60
Monocytes (percent)	2.2 ± 0.33	2.4 ± 0.43	2.2 ± 0.36	2.6 ± 0.45	1.0 ± 0.26	2.7 ± 0.26
Eosinophils (percent)	0.4 ± 0.22	0.6 ± 0.22	1.1 ± 0.38	0.6 ± 0.22	1.1 ± 0.35	0.6 ± 0.31
Hematocrit (percent)	48.4 ± 1.33	49.4 ± 0.66	49.5 ± 0.93	49.8 ± 0.97	48.5 ± 1.01	49.5 ± 0.70
Hemoglobin (g/dl)	16.4 ± 0.36	16.9 ± 0.21	16.8 ± 0.20	17.0 ± 0.32	16.2 ± 0.44	16.7 ± 0.20
Mean corpuscular hemoglobin (pg)	22.8 ± 0.08	22.8 ± 0.13	22.6 ± 0.14	22.5 ± 0.13	*22.0 ± 0.38	*22.4 ± 0.13
Mean corpuscular hemoglobin concentration (g/dl)	33.9 ± 0.32	34.1 ± 0.43	33.9 ± 0.39	34.1 ± 0.45	33.4 ± 0.73	33.8 ± 0.35
Mean cell volume (cubic microns)	67.3 ± 0.45	66.8 ± 0.57	66.7 ± 0.40	66.1 ± 0.53	66.1 ± 0.48	66.3 ± 0.47
Methemoglobin (g/dl)	1.19 ± 0.300	1.28 ± 0.301	0.68 ± 0.187	1.15 ± 0.318	0.91 ± 0.232	0.79 ± 0.244
Platelets (10^3/mm^3)	577 ± 22.6	573 ± 32.9	541 ± 19.3	(c) 582 ± 19.1	544 ± 12.7	564 ± 20.3
Erythrocytes (10^6/mm^3)	7.18 ± 0.164	7.40 ± 0.078	7.42 ± 0.110	7.53 ± 0.124	7.35 ± 0.140	7.46 ± 0.079
Reticulocytes (10^6/mm^3)	3.10 ± 0.343	3.97 ± 0.295	3.04 ± 0.387	2.96 ± 0.240	3.72 ± 0.321	3.38 ± 0.252
Albumin/globulin ratio	1.11 ± 0.018	1.12 ± 0.039	1.12 ± 0.025	1.11 ± 0.018	1.16 ± 0.022	1.15 ± 0.027
Albumin (g/dl)	3.66 ± 0.060	3.74 ± 0.040	3.64 ± 0.040	3.69 ± 0.046	3.50 ± 0.052	3.53 ± 0.033
Urea nitrogen (mg/dl)	17.8 ± 1.07	18.7 ± 0.65	16.5 ± 0.50	16.3 ± 0.49	16.3 ± 0.80	16.2 ± 0.91
Calcium (mg/dl)	10.5 ± 0.11	10.8 ± 0.11	10.6 ± 0.05	10.7 ± 0.12	10.2 ± 0.14	10.4 ± 0.11
Chloride (meq/liter)	106 ± 1.5	105 ± 1.1	106 ± 1.1	106 ± 1.4	106 ± 0.9	106 ± 1.1
Cholinesterase (IU/liter)	3,701 ± 83	3,644 ± 78	*3,166 ± 209	**2,997 ± 205	**1,798 ± 162	**1,702 ± 163
Creatinine (mg/dl)	0.47 ± 0.015	0.51 ± 0.028	0.46 ± 0.027	0.48 ± 0.029	0.47 ± 0.026	0.50 ± 0.026
GGT (IU/liter)	1.4 ± 0.16	1.5 ± 0.17	1.4 ± 0.22	1.6 ± 0.22	1.3 ± 0.15	1.5 ± 0.17
Inorganic phosphorus (mg/dl)	6.31 ± 0.198	6.38 ± 0.118	5.84 ± 0.236	6.43 ± 0.216	6.08 ± 0.243	6.43 ± 0.222
Potassium (meq/liter)	5.21 ± 0.084	5.29 ± 0.091	5.20 ± 0.098	5.46 ± 0.127	5.14 ± 0.064	5.48 ± 0.165
Glucose (mg/dl)	131 ± 2.0	134 ± 2.7	137 ± 2.4	134 ± 3.2	133 ± 3.0	134 ± 3.0
Sodium (meq/liter)	144 ± 1.1	145 ± 0.8	145 ± 1.1	146 ± 1.3	145 ± 0.9	146 ± 1.1
Total bilirubin (mg/dl)	0.15 ± 0.017	0.19 ± 0.018	0.15 ± 0.022	0.17 ± 0.021	0.13 ± 0.015	0.15 ± 0.022
Total protein (g/dl)	6.98 ± 0.107	7.09 ± 0.087	6.92 ± 0.090	7.02 ± 0.079	**6.53 ± 0.110	*6.61 ± 0.075

(a) Mean ± standard error. P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977). GGT = γ-glutamyl transferase; cholinesterase activity was measured in plasma; IU = international units.
(b) Except as noted
(c) Nine animals were examined.
*$P < 0.05$
**$P < 0.01$

TABLE H3. HEMATOLOGIC DATA FOR RATS IN THE FIFTEEN-MONTH INHALATION STUDIES OF TOLUENE (a)

Analysis	Control	600 ppm	1,200 ppm
MALE			
Leukocytes (1,000/µl)	5.9 ± 0.43	6.2 ± 0.39	6.9 ± 0.36
Lymphocytes (1,000/µl)	3.4 ± 0.31	3.9 ± 0.27	3.8 ± 0.32
Segmented neutrophils (1,000/µl)	2.2 ± 0.27	2.1 ± 0.22	2.8 ± 0.40
Monocytes (1,000/µl)	(b) 0.11 ± 0.011	(b) 0.13 ± 0.024	(c) 0.20 ± 0.053
Eosinophils (1,000/µl)	0.16 ± 0.027	(d) 0.18 ± 0.025	(e) 0.22 ± 0.040
Hematocrit (percent)	49.6 ± 0.75	50.4 ± 0.88	49.0 ± 1.25
Hemoglobin (g/dl)	18.3 ± 0.23	18.6 ± 0.32	18.2 ± 0.49
Methemoglobin (g/dl)	0.35 ± 0.031	(b) 0.30 ± 0.032	0.35 ± 0.044
Mean corpuscular hemoglobin (pg)	20.0 ± 0.18	19.8 ± 0.10	19.4 ± 0.30
Mean corpuscular hemoglobin concentration (g/dl)	37.0 ± 0.25	36.8 ± 0.10	37.2 ± 0.25
Mean cell volume (μ^3)	54.1 ± 0.64	53.4 ± 0.34	*52.2 ± 0.66
Nucleated erythrocytes (1,000/µl)	0.08 ± 0.034	0.03 ± 0.017	0.01 ± 0.005
Erythrocytes (10^6/µl)	9.2 ± 0.08	9.4 ± 0.20	9.4 ± 0.19
FEMALE			
Leukocytes (1,000/µl)	3.9 ± 0.39	3.5 ± 0.21	3.7 ± 0.21
Lymphocytes (1,000/µl)	2.5 ± 0.17	2.4 ± 0.16	2.5 ± 0.14
Segmented neutrophils (1,000/µl)	1.4 ± 0.32	1.0 ± 0.08	1.0 ± 0.10
Monocytes (1,000/µl)	(e) 0.10 ± 0.00	(f) 0.10 ± 0.00	(d) 0.10 ± 0.00
Eosinophils (1,000/µl)	(d) 0.10 ± 0.00	(c) 0.10 ± 0.00	(e) 0.18 ± 0.040
Hematocrit (percent)	48.6 ± 0.69	47.7 ± 0.34	48.4 ± 0.58
Hemoglobin (g/dl)	18.1 ± 0.23	17.7 ± 0.16	17.9 ± 0.21
Methemoglobin (g/dl)	0.26 ± 0.015	0.32 ± 0.042	0.30 ± 0.030
Mean corpuscular hemoglobin (pg)	21.8 ± 0.13	21.8 ± 0.09	21.6 ± 0.11
Mean corpuscular hemoglobin concentration (g/dl)	37.1 ± 0.14	37.0 ± 0.17	37.1 ± 0.15
Mean cell volume (μ^3)	58.8 ± 0.29	58.7 ± 0.30	58.4 ± 0.27
Nucleated erythrocytes (1,000/µl)	0.06 ± 0.016	0.06 ± 0.017	0.03 ± 0.011
Erythrocytes (10^6/µl)	8.3 ± 0.12	8.1 ± 0.09	8.3 ± 0.10

(a) Mean ± standard error for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine animals were examined.
(c) Seven animals were examined.
(d) Eight animals were examined.
(e) Six animals were examined.
(f) Five animals were examined.
*$P<0.05$

TABLE H4. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE (a)

Analysis	Vehicle Control	312 mg/kg	625 mg/kg	1,250 mg/kg	2,500 mg/kg
MALE					
Number examined (b)	10	10	10	10	6
Eosinophils (10^3/mm^3)	0.04 ± 0.019	0.09 ± 0.043	0.05 ± 0.019	0.01 ± 0.008	(c) 0.08 ± 0.055
Hematocrit (percent)	38.4 ± 0.41	36.9 ± 0.68	37.8 ± 0.39	38.0 ± 0.32	37.4 ± 0.64
Hemoglobin (g/dl)	14.9 ± 0.22	14.4 ± 0.25	14.9 ± 0.15	14.9 ± 0.19	14.8 ± 0.20
Lymphocytes (10^3/mm^3)	2.75 ± 0.321	2.98 ± 0.668	3.11 ± 0.346	2.50 ± 0.464	2.89 ± 0.382
Mean corpuscular hemoglobin (pg)	18.9 ± 0.23	19.1 ± 0.16	19.2 ± 0.12	19.3 ± 0.13	19.2 ± 0.04
Mean corpuscular hemoglobin concentration (g/dl)	38.8 ± 0.40	39.1 ± 0.32	39.5 ± 0.37	39.2 ± 0.42	39.6 ± 0.34
Mean cell volume (cubic microns)	48.6 ± 0.27	48.8 ± 0.53	48.7 ± 0.30	49.5 ± 0.40	48.3 ± 0.56
Methemoglobin (percent)	7.57 ± 1.205	12.12 ± 1.303	6.24 ± 1.301	6.21 ± 1.379	(d) 6.16 ± 2.997
Monocytes 10^3/mm^3)	0.07 ± 0.017	0.07 ± 0.022	0.07 ± 0.014	0.07 ± 0.017	(c) 0.11 ± 0.033
Platelets (10^3/mm^3)	864 ± 20.6	865 ± 45.8	798 ± 36.8	863 ± 54.1	809 ± 74.0
Erythrocytes (10^6/mm^3)	7.89 ± 0.062	*7.56 ± 0.096	7.76 ± 0.064	7.71 ± 0.076	7.72 ± 0.110
Reticulocytes (percent)	(e) 4.57 ± 0.570	(c) 3.38 ± 0.410	(f) 4.11 ± 0.275	(g) 3.70 ± 0.473	(c) 3.88 ± 0.265
Segmented neutrophils (10^3/mm^3)	0.75 ± 0.083	0.80 ± 0.200	0.87 ± 0.097	0.50 ± 0.082	0.93 ± 0.090
Leukocytes (10^3/mm^3)	3.61 ± 0.382	3.95 ± 0.893	4.11 ± 0.391	3.08 ± 0.557	4.02 ± 0.450
Albumin (g/dl)	(f) 3.58 ± 0.073	(f) 3.56 ± 0.094	3.52 ± 0.047	3.52 ± 0.036	(c) 3.78 ± 0.162
Blood urea nitrogen (mg/dl)	(f) 20.3 ± 1.32	(f) 23.3 ± 3.88	19.6 ± 0.69	19.0 ± 0.47	(c) 18.6 ± 1.70
Calcium (mg/dl)	(g) 10.8 ± 0.23	(e) 11.1 ± 0.30	(f) 10.8 ± 0.22	(f) 11.3 ± 0.18	*(h) 14.2 ± 1.95
Lactic dehydrogenase (IU/liter)	(f) 928 ± 89.9	(f) 908 ± 101.8	754 ± 104.7	837 ± 102.7	(c) 990 ± 167.1
Inorganic phosphorus (mg/dl)	(e) 9.78 ± 0.535	(e) 10.33 ± 0.868	(f) 9.90 ± 0.387	(f) 9.99 ± 0.753	(h) 9.15 ± 3.050
Total protein (g/dl)	(g) 6.91 ± 0.108	(f) 7.05 ± 0.304	7.10 ± 0.136	(f) 7.13 ± 0.164	(h) 7.50 ± 0.100
FEMALE					
Number examined (b)	10	10	10	9	6
Eosinophils (10^3/mm^3)	0.03 ± 0.018	0.06 ± 0.015	0.02 ± 0.010	(f) 0.06 ± 0.021	*(c) 0.07 ± 0.018
Hematocrit (percent)	38.4 ± 0.38	37.7 ± 0.56	38.4 ± 0.59	37.6 ± 0.71	37.9 ± 0.30
Hemoglobin (g/dl)	14.8 ± 0.14	14.5 ± 0.11	14.8 ± 0.14	14.6 ± 0.23	14.9 ± 0.09
Lymphocytes (10^3/mm^3)	3.12 ± 1.420	2.45 ± 0.225	2.20 ± 0.436	(f) 2.34 ± 0.236	(c) 3.19 ± 0.355
Mean corpuscular hemoglobin (pg)	19.1 ± 0.11	19.1 ± 0.09	19.3 ± 0.04	19.3 ± 0.12	*19.4 ± 0.14
Mean corpuscular hemoglobin concentration (g/dl)	38.6 ± 0.36	38.5 ± 0.33	38.6 ± 0.35	38.7 ± 0.37	39.3 ± 0.25
Mean cell volume (cubic microns)	49.8 ± 0.51	49.5 ± 0.52	50.0 ± 0.47	49.9 ± 0.26	49.7 ± 0.33
Methemoglobin (percent)	9.62 ± 1.532	10.05 ± 1.777	7.51 ± 1.628	(f) 6.53 ± 1.301	(c) 5.88 ± 1.946
Monocytes 10^3/mm^3)	0.04 ± 0.012	0.06 ± 0.011	0.07 ± 0.020	0.07 ± 0.017	(c) 0.07 ± 0.017
Platelets (10^3/mm^3)	756 ± 25.2	801 ± 27.0	795 ± 30.6	739 ± 55.4	*838 ± 36.9
Erythrocytes (10^6/mm^3)	7.75 ± 0.077	7.58 ± 0.057	7.69 ± 0.068	7.56 ± 0.123	7.67 ± 0.073
Reticulocytes (percent)	(e) 3.05 ± 0.593	(e) 2.72 ± 0.634	(g) 4.07 ± 0.275	(g) 4.04 ± 0.428	3.40 ± 0.465
Segmented neutrophils (10^3/mm^3)	0.78 ± 0.150	0.83 ± 0.128	0.83 ± 0.092	0.73 ± 0.053	(c) 1.06 ± 0.140
Leukocytes (10^3/mm^3)	3.97 ± 1.569	3.39 ± 0.265	3.12 ± 0.486	3.23 ± 0.286	4.18 ± 0.452
Albumin (g/dl)	3.58 ± 0.083	3.56 ± 0.034	(i) 3.69 ± 0.070	*(f) 3.80 ± 0.060	3.80 ± 0.086
Blood urea nitrogen (mg/dl)	19.9 ± 0.72	**15.9 ± 0.42	**(i) 17.5 ± 0.65	*(f) 17.9 ± 1.28	*16.7 ± 0.39
Calcium (mg/dl)	(i) 10.7 ± 0.15	(i) 10.3 ± 0.22	(g) 10.5 ± 0.22	(e) 11.0 ± 0.19	**11.9 ± 0.18
Lactic dehydrogenase (IU/liter)	628 ± 48.8	580 ± 31.5	(f) 683 ± 58.7	(g) 649 ± 81.4	694 ± 99.3
Inorganic phosphorus (mg/dl)	(i) 9.64 ± 0.701	9.34 ± 0.568	(g) 8.56 ± 0.241	(e) 9.22 ± 0.601	10.87 ± 0.650
Total protein (g/dl)	(i) 6.37 ± 0.177	6.30 ± 0.087	(f) 6.75 ± 0.217	(e) 6.63 ± 0.079	*7.12 ± 0.218

(a) Mean ± standard error. P values are vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977). IU = international units.
(b) Except as noted
(c) Five animals were examined.
(d) Four animals were examined.
(e) Six animals were examined.
(f) Eight animals were examined.
(g) Seven animals were examined.
(h) Two animals were examined.
(i) Nine animals were examined.
*P<0.05
**P<0.01

TABLE H5. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MICE IN THE FOURTEEN-WEEK INHALATION STUDIES OF TOLUENE (a)

Analysis	Control	100 ppm	625 ppm	1,250 ppm	2,500 ppm	3,000 ppm
MALE						
Number examined (b)	10	10	10	10	10	4
Leukocytes ($10^3/mm^3$)	5.17 ± 0.791	4.93 ± 0.593	3.96 ± 0.454	5.31 ± 0.495	5.10 ± 0.673	4.73 ± 1.018
Lymphocytes (percent)	77.9 ± 1.72	75.9 ± 3.66	76.9 ± 4.19	78.7 ± 2.95	73.2 ± 2.14	78.8 ± 3.09
Segmented neutrophils (percent)	17.1 ± 1.74	19.1 ± 3.53	20.2 ± 4.38	16.5 ± 2.73	22.8 ± 2.31	17.0 ± 3.63
Monocytes (percent)	2.3 ± 0.34	2.6 ± 0.50	1.6 ± 0.31	2.2 ± 0.47	2.1 ± 0.53	2.0 ± 1.00
Eosinophils (percent)	2.4 ± 0.45	2.2 ± 0.59	1.0 ± 0.26	2.4 ± 0.40	1.7 ± 0.30	2.3 ± 1.11
Hematocrit (percent)	42.1 ± 0.56	41.9 ± 0.35	41.8 ± 0.64	42.2 ± 0.59	42.3 ± 0.47	41.9 ± 0.74
Hemoglobin (g/dl)	17.1 ± 0.18	16.9 ± 0.19	16.9 ± 0.26	16.7 ± 0.14	17.0 ± 0.23	16.6 ± 0.3
Mean corpuscular hemoglobin (pg)	20.0 ± 0.10	19.7 ± 0.17	20.0 ± 0.18	19.8 ± 0.21	20.2 ± 0.17	20.0 ± 0.21
Mean corpuscular hemoglobin concentration (g/dl)	40.7 ± 0.43	40.3 ± 0.49	40.4 ± 0.52	39.8 ± 0.56	40.2 ± 0.48	39.6 ± 0.55
Mean cell volume (cubic microns)	49.1 ± 0.41	49.0 ± 0.30	49.4 ± 0.34	49.9 ± 0.38	*50.3 ± 0.30	50.5 ± 0.65
Methemoglobin (g/dl)	0.76 ± 0.187	0.45 ± 0.115	0.73 ± 0.135	0.65 ± 0.182	0.53 ± 0.131	0.64 ± 0.213
Platelets ($10^3/mm^3$)	565 ± 49.8	600 ± 26.4	664 ± 17.2	666 ± 27.0	661 ± 33.6	507 ± 170.8
Erythrocytes ($10^6/mm^3$)	8.60 ± 0.100	8.55 ± 0.070	8.47 ± 0.130	8.47 ± 0.109	8.42 ± 0.105	8.31 ± 0.096
Reticulocytes ($10^6/mm^3$)	4.30 ± 0.402	5.04 ± 0.488	4.18 ± 0.383	4.68 ± 0.421	4.50 ± 0.287	3.98 ± 0.719
Albumin/globulin ratio	1.18 ± 0.025	1.20 ± 0.030	1.17 ± 0.026	1.16 ± 0.031	*1.10 ± 0.015	*1.08 ± 0.048
Albumin (g/dl)	3.37 ± 0.063	3.35 ± 0.045	3.34 ± 0.048	3.16 ± 0.064	3.35 ± 0.069	3.40 ± 0.041
Urea nitrogen (mg/dl)	24.1 ± 1.36	24.5 ± 1.42	24.8 ± 1.88	23.9 ± 1.25	23.1 ± 1.15	(c) 23.3 ± 1.65
Calcium (mg/dl)	9.98 ± 0.131	10.03 ± 0.097	9.99 ± 0.085	9.74 ± 0.183	*10.63 ± 0.184	*(c) 11.03 ± 0.219
Creatinine (mg/dl)	0.15 ± 0.031	0.15 ± 0.027	0.11 ± 0.010	0.15 ± 0.027	0.15 ± 0.027	(c) 0.10 ± 0.000
GGT (IU/liter)	1.30 ± 0.300	1.10 ± 0.100	1.10 ± 0.100	1.30 ± 0.213	1.00 ± 0.000	1.25 ± 0.250
Inorganic phosphorus (mg/dl)	10.0 ± 0.32	10.1 ± 0.46	10.3 ± 0.36	9.3 ± 0.35	10.6 ± 0.40	(c) 11.3 ± 0.37
Glucose (mg/dl)	159 ± 5.0	143 ± 7.1	153 ± 7.6	145 ± 3.7	(d) 144 ± 6.5	(c) 152 ± 11.2
Total bilirubin (mg/dl)	0.30 ± 0.037	0.31 ± 0.018	0.33 ± 0.030	0.32 ± 0.025	(e) 0.42 ± 0.039	(c) 0.40 ± 0.058
Total protein (g/dl)	6.21 ± 0.087	6.15 ± 0.093	6.20 ± 0.082	5.89 ± 0.126	6.42 ± 0.117	6.63 ± 0.149
FEMALE						
Number examined (b)	10	10	9	9	3	0
Leukocytes ($10^3/mm^3$)	3.63 ± 0.447	3.40 ± 0.315	3.09 ± 0.551	3.07 ± 0.376	3.50 ± 1.185	--
Lymphocytes (percent)	78.7 ± 2.44	(d) 81.8 ± 2.40	80.3 ± 1.67	82.4 ± 1.20	78.7 ± 2.40	--
Segmented neutrophils (percent)	17.2 ± 2.31	(d) 15.4 ± 2.09	16.9 ± 1.74	14.9 ± 1.29	16.3 ± 2.96	--
Monocytes (percent)	2.4 ± 0.34	1.9 ± 0.35	1.8 ± 0.47	1.4 ± 0.38	2.7 ± 0.33	--
Eosinophils (percent)	1.7 ± 0.37	*0.5 ± 0.40	1.0 ± 0.29	(e) 1.1 ± 0.30	2.3 ± 1.33	--
Hematocrit (percent)	41.9 ± 0.34	42.0 ± 0.41	42.5 ± 0.45	42.4 ± 0.56	41.1 ± 0.59	--
Hemoglobin (g/dl)	16.7 ± 0.14	16.9 ± 0.13	17.0 ± 0.14	*17.1 ± 0.12	16.4 ± 0.27	--
Mean corpuscular hemoglobin (pg)	20.0 ± 0.18	20.2 ± 0.21	20.3 ± 0.20	20.6 ± 0.24	20.3 ± 0.54	--
Mean corpuscular hemoglobin concentration (g/dl)	39.8 ± 0.48	40.3 ± 0.54	39.9 ± 0.55	40.4 ± 0.57	40.1 ± 1.23	--
Mean cell volume (cubic microns)	50.2 ± 0.33	50.1 ± 0.43	51.0 ± 0.37	50.9 ± 0.45	50.7 ± 0.33	--
Methemoglobin (g/dl)	0.54 ± 0.149	0.74 ± 0.149	0.39 ± 0.112	0.65 ± 0.145	1.11 ± 0.244	--
Platelets ($10^3/mm^3$)	663 ± 14.2	638 ± 26.7	663 ± 33.6	676 ± 29.2	667 ± 50.0	--
Erythrocytes ($10^6/mm^3$)	8.35 ± 0.063	8.37 ± 0.070	8.34 ± 0.047	8.34 ± 0.094	8.12 ± 0.082	--
Reticulocytes ($10^6/mm^3$)	4.86 ± 0.415	4.41 ± 0.372	4.27 ± 0.448	4.04 ± 0.554	4.33 ± 0.636	--
Albumin/globulin ratio	1.36 ± 0.040	1.41 ± 0.038	1.37 ± 0.047	1.29 ± 0.045	1.17 ± 0.067	--
Albumin (g/dl)	3.46 ± 0.034	3.53 ± 0.054	3.41 ± 0.039	3.40 ± 0.075	3.37 ± 0.120	--
Urea nitrogen (mg/dl)	20.5 ± 1.08	21.8 ± 1.02	20.6 ± 1.37	19.8 ± 1.54	21.9 ± 2.24	--
Calcium (mg/dl)	10.02 ± 0.140	10.02 ± 0.090	9.82 ± 0.090	(e) 10.06 ± 0.120	10.93 ± 0.190	--
Creatinine (mg/dl)	0.13 ± 0.030	0.13 ± 0.015	0.20 ± 0.041	0.13 ± 0.024	0.20 ± 0.100	--
GGT (IU/liter)	1.00 ± 0.000	1.00 ± 0.000	1.00 ± 0.000	1.11 ± 0.111	1.00 ± 0.000	--
Inorganic phosphorus (mg/dl)	9.8 ± 0.30	10.5 ± 0.57	9.9 ± 0.26	10.3 ± 0.41	10.9 ± 0.77	--
Glucose (mg/dl)	138 ± 6.2	143 ± 4.7	144 ± 7.9	(e) 154 ± 7.7	132 ± 10.0	--
Total bilirubin (mg/dl)	0.28 ± 0.025	0.24 ± 0.027	0.23 ± 0.017	0.24 ± 0.018	0.37 ± 0.067	--
Total protein (g/dl)	5.99 ± 0.071	6.07 ± 0.084	5.94 ± 0.060	6.03 ± 0.099	6.17 ± 0.088	--

(a) Mean ± standard error. P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977). GGT = γ-glutamyl transferase; IU = international units.
(b) Except as noted
(c) Three animals were examined.
(d) Nine animals were examined.
(e) Eight animals were examined
*$P < 0.05$

TABLE H6. HEMATOLOGIC DATA FOR FEMALE MICE IN THE FIFTEEN-MONTH INHALATION STUDY OF TOLUENE (a)

Analysis	Control	120 ppm	600 ppm	1,200 ppm
Number examined (b)	10	10	9	10
Leukocytes (1,000/µl)	3.6 ± 0.41	3.9 ± 0.32	3.5 ± 0.32	4.0 ± 0.51
Lymphocytes (1,000/µl)	2.5 ± 0.32	2.7 ± 0.13	2.4 ± 0.24	2.7 ± 0.30
Segmented neutrophils (1,000/µl)	0.94 ± 0.129	1.10 ± 0.256	0.96 ± 0.113	1.18 ± 0.207
Monocytes (1,000/µl)	(c) 0.18 ± 0.049	(d) 0.11 ± 0.014	(c) 0.11 ± 0.012	(c) 0.15 ± 0.038
Eosinophils (1,000/µl)	(e) 0.10 ± 0.000	(f) 0.15 ± 0.029	(e) 0.12 ± 0.017	(g) 0.10 ± 0.000
Hematocrit (percent)	45.1 ± 2.32	42.6 ± 0.58	43.8 ± 0.60	45.1 ± 0.78
Hemoglobin (g/dl)	15.8 ± 0.45	15.3 ± 0.11	15.6 ± 0.10	15.7 ± 0.16
Methemoglobin (g/dl)	0.22 ± 0.062	0.36 ± 0.175	0.35 ± 0.063	0.34 ± 0.086
Mean corpuscular hemoglobin (pg)	19.7 ± 0.20	19.3 ± 0.14	19.6 ± 0.18	19.5 ± 0.34
Mean corpuscular hemoglobin concentration (g/dl)	36.4 ± 0.52	36.0 ± 0.39	35.6 ± 0.41	34.9 ± 0.57
Mean cell volume (μ^3)	54.1 ± 0.64	53.6 ± 0.69	55.1 ± 0.70	56.0 ± 1.61
Erythrocytes (10^6/µl)	8.3 ± 0.45	7.9 ± 0.11	8.0 ± 0.11	8.1 ± 0.23

(a) Mean ± standard error; no significant differences vs. the controls were observed by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Except as noted
(c) Eight animals were examined.
(d) Seven animals were examined.
(e) Six animals were examined.
(f) Four animals were examined.
(g) Five animals were examined.

TABLE H7. ORGAN WEIGHTS OF RATS IN THE FIFTEEN-MONTH INHALATION STUDIES OF TOLUENE (a)

Organ	Control	600 ppm	1,200 ppm
MALE			
Body weight (grams)	400 ± 13.4	397 ± 11.4	364 ± 11.9
Right kidney			
Absolute	1,327 ± 60	1,378 ± 37	1,283 ± 49
Relative	3.3 ± 0.10	3.5 ± 0.09	3.5 ± 0.08
Liver			
Absolute	(b) 13,770 ± 440	13,320 ± 620	12,280 ± 530
Relative	34.7 ± 1.18	33.9 ± 1.82	33.7 ± 0.99
Brain			
Absolute	1,944 ± 20	1,973 ± 32	1,873 ± 23
Relative	5.0 ± 0.18	5.0 ± 0.16	5.2 ± 0.16
FEMALE			
Body weight (grams)	242 ± 3.1	266 ± 9.0	238 ± 9.0
Right kidney			
Absolute	860 ± 23	880 ± 23	(b) 854 ± 27
Relative	3.6 ± 0.08	3.3 ± 0.08	(b) 3.6 ± 0.09
Liver			
Absolute	8,062 ± 340	*10,409 ± 913	8,486 ± 283
Relative	33.3 ± 1.19	40.1 ± 4.83	35.8 ± 0.72
Brain			
Absolute	1,754 ± 27	1,852 ± 57	1,783 ± 23
Relative	7.3 ± 0.12	7.0 ± 0.28	7.6 ± 0.27

(a) Mean ± standard error in milligrams per gram (relative) or milligrams (absolute) for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine organs were weighed.
*P<0.05

TABLE H8. ORGAN WEIGHTS OF FEMALE MICE IN THE FIFTEEN-MONTH INHALATION STUDY OF TOLUENE (a)

Organ	Control	120 ppm	600 ppm	1,200 ppm
Body weight (grams)	34.9 ± 1.83	33.4 ± 1.83	35.1 ± 1.88	32.0 ± 0.68
Brain				
Absolute	497 ± 5.1	487 ± 10.5	498 ± 9.9	492 ± 11.8
Relative	14.5 ± 0.61	15.0 ± 0.87	14.5 ± 0.67	15.5 ± 0.54
Right kidney				
Absolute	285 ± 12.7	272 ± 13.9	285 ± 10.4	280 ± 16.8
Relative	8.2 ± 0.34	8.2 ± 0.30	8.2 ± 0.32	8.8 ± 0.61
Liver				
Absolute	1,854 ± 99	1,903 ± 89	1,920 ± 70	1,920 ± 105
Relative	54.3 ± 3.89	57.5 ± 2.19	55.2 ± 1.67	60.4 ± 3.81

(a) Mean ± standard error in milligrams per gram (relative) or milligrams (absolute) for groups of 10 animals; no significant differences vs. the controls were observed by Dunn's test (Dunn, 1964).

APPENDIX I

CHEMICAL CHARACTERIZATION, ANALYSIS, AND GENERATION OF CHAMBER CONCENTRATIONS OF TOLUENE FOR THE TOXICOLOGY STUDIES

APPENDIX I. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Toluene

Toluene was obtained in one lot (lot no. H-12-19-80) from Exxon Company, USA (Baytown, TX) as a clear, colorless liquid and was received in sixteen 55-gallon drums. Purity and identity analyses were conducted on representative samples at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the toluene studies are on file at the National Institute of Environmental Health Sciences.

The study material was identified as toluene by spectroscopic analyses. The infrared (Figure I1), ultraviolet/visible, and nuclear magnetic resonance (Figure I2) spectra were consistent with the literature spectra (Sadtler Standard Spectra) and with those expected for the structure.

The purity of toluene was determined by elemental analysis, Karl Fischer water analysis, and gas chromatography. Gas chromatographic analysis was performed with flame ionization detection and a nitrogen carrier with a flow rate of 70 ml/minute with either a 0.1% SP1000 (system 1) or a 20% SP2100/0.1% Carbowax 1500 (system 2) column. Benzene was identified as an impurity by spiking and was quantitated against standard benzene solutions with gas chromatographic system 2. The results of elemental analyses for carbon and hydrogen were in agreement with the theoretical values. Karl Fischer analysis indicated the presence of 0.047% water. Gas chromatography by both systems detected three impurities with individual peak areas less than 0.1% of the major peak area. Benzene was present as an impurity at 5.7 ppm (v/v). The data indicated that lot no. H-12-19-80 was greater than 99% pure.

Stability studies performed by gas chromatography with system 1 (with chlorobenzene as an internal standard) indicated that toluene was stable as a bulk chemical when stored for 2 weeks protected from light at temperatures up to 60° C.

Periodic analysis of lot no. H-12-19-80 for purity by gas chromatography and ultraviolet spectroscopy and for identity by infrared spectroscopy indicated no apparent degradation of the study material throughout the studies.

Preparation and Characterization of Dose Mixtures

The appropriate amounts of toluene and corn oil were mixed (w/v) to give the desired concentrations. The stability of toluene in corn oil was determined after the sample was extracted with methanol by gas chromatography with flame ionization detection and with the same column as system 2 but at a flow rate of 30 ml/minute and with nonane as an internal standard. Toluene dissolved in corn oil at 20 mg/ml was found to be stable at 5° C and at room temperature in the dark for 2 weeks. Solutions exposed to air and light for 3 hours were chemically stable, but a 23% loss due to evaporation was observed over the 3-hour period. Dose mixtures were stored at room temperature protected from light in Nalgene® bottles for no longer than 2 weeks throughout the studies. Dose mixtures were analyzed several times during the 13-week studies, and concentrations ranged from 91% to 107% of the target concentrations (Table I1).

Generation and Measurement of Chamber Concentrations

Vapor Generation System

Liquid toluene was delivered by a pump from a stainless steel safety can through Teflon® tubing to a Spraying Systems® atomizer (Figure I3) that was operated with nitrogen. Nitrogen and the atomizer were heated to approximately 80° C with a 400-W cartridge heater. The toluene was sprayed into a

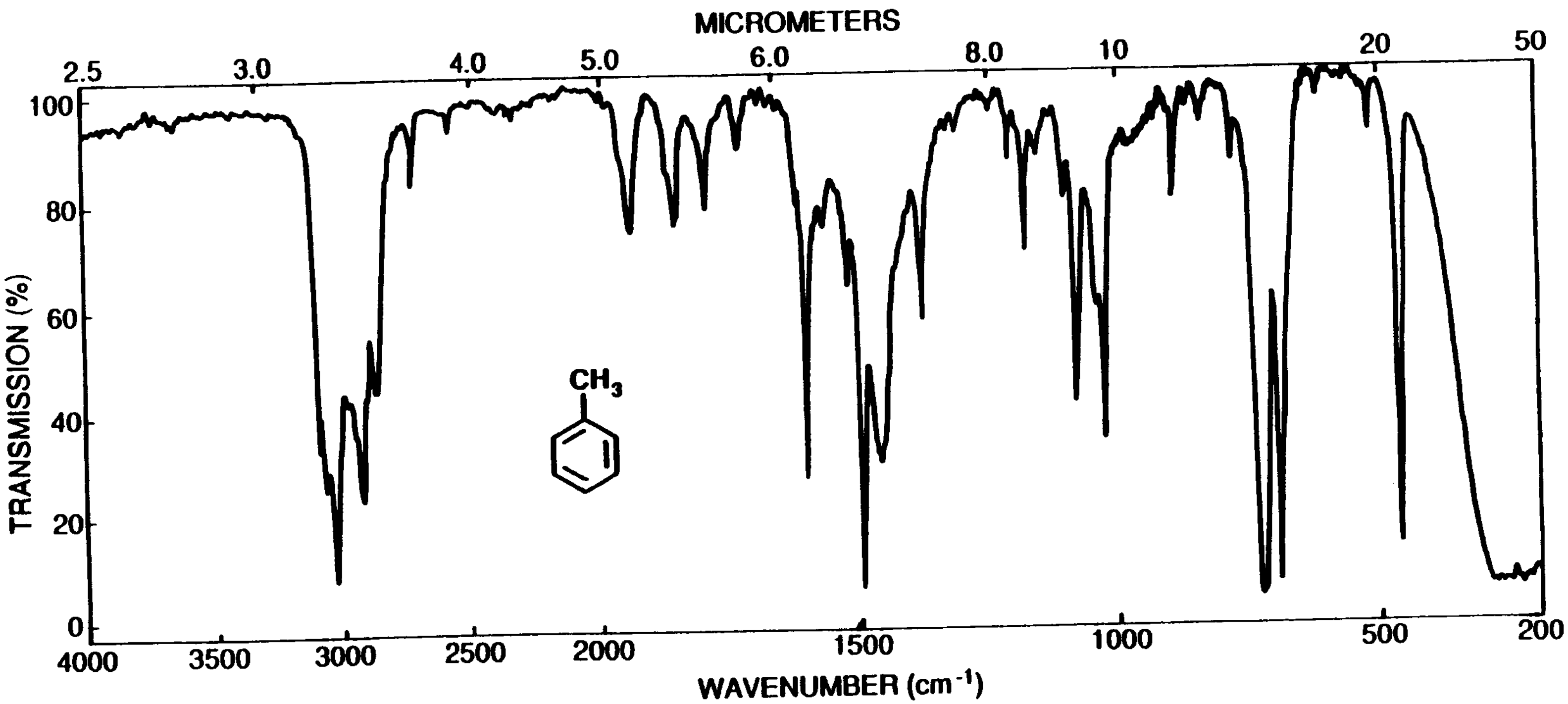

FIGURE I1. INFRARED ABSORPTION SPECTRUM OF TOLUENE (LOT NO. H-12-19-80)

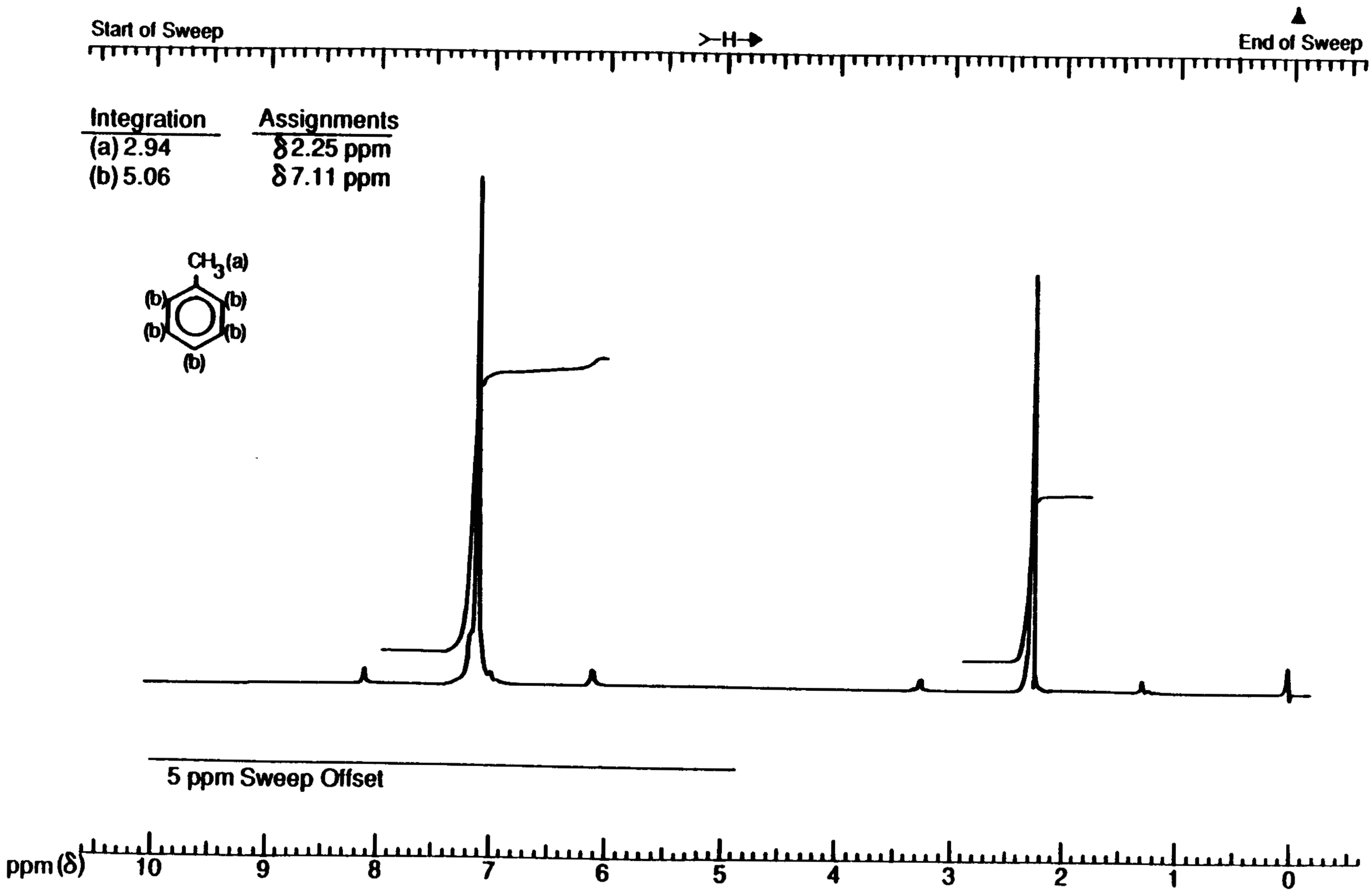

FIGURE 12. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF TOLUENE (LOT NO. H-12-19-80)

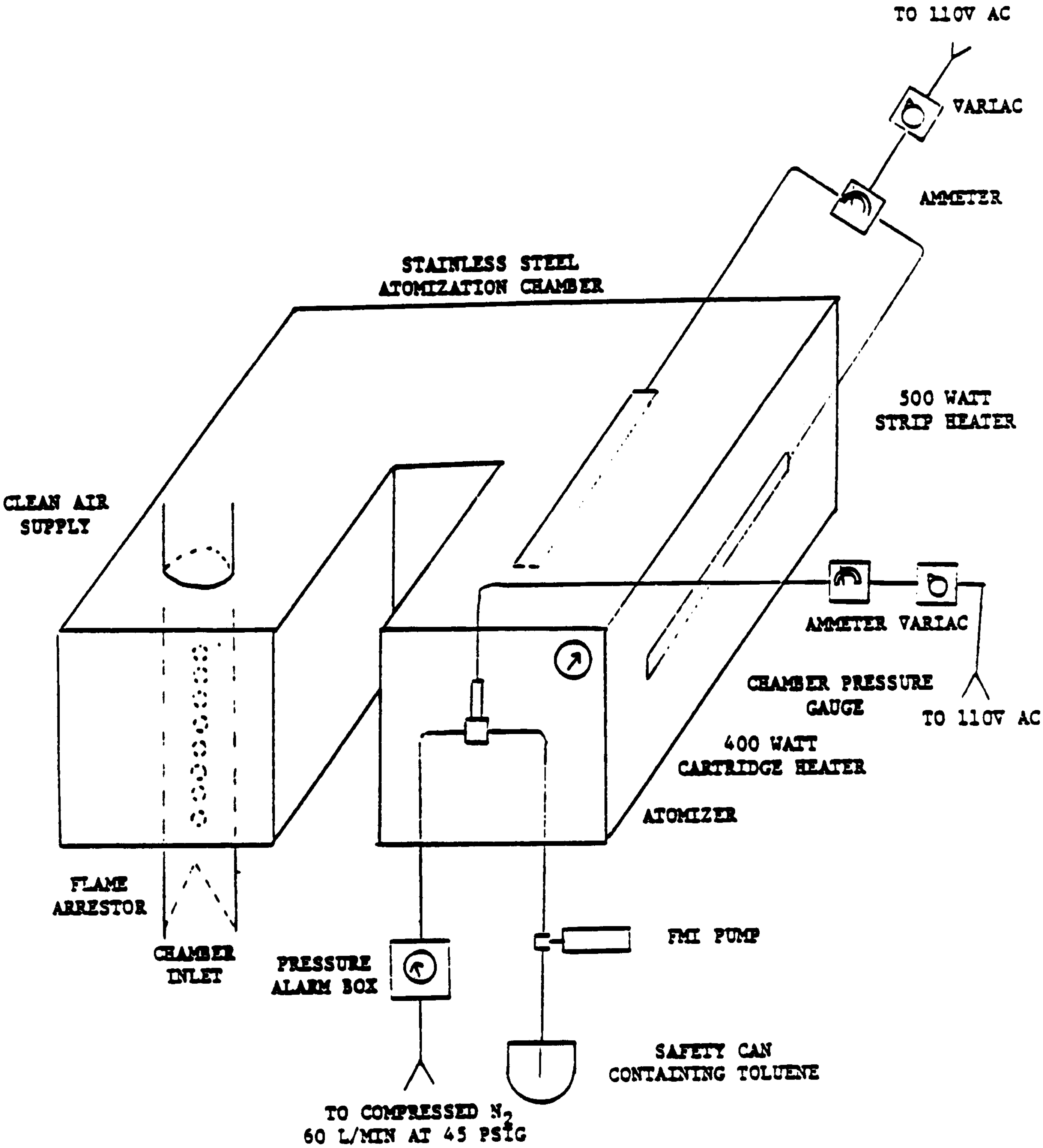

FIGURE I3. TOLUENE VAPOR GENERATION SYSTEM

TABLE I1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF TOLUENE

Date Mixed	Concentration of Toluene in Corn Oil (mg/ml) Target	Determined (a)	Determined as a Percent of Target
05/18/81	31.2	28.4	91
	62.5	57.2	92
	125	116	93
	250	239	96
	500	488	98
05/20/81	31.2	29.5	95
	62.5	59.4	96
	125	118	94
	250	240	96
	500	489	98
06/29/81	62.5	57.7	92
	125	119	95
	250	237	95
06/30/81	31.2	28.6	92
07/01/81	31.2	32.7	105
	62.5	65.2	104
	125	134	107
	250	(b) 260	104
07/13/81	31.2	30.0	96

(a) Results of duplicate analysis, except as noted
(b) Average of two duplicate analyses

U-shaped stainless steel atomization chamber. For high dose groups, the atomization chamber walls were also heated by four 500-W strip heaters to a surface temperature of 85° C to increase the rate of vaporization. Toluene vapors flowed into a pipe extending through one end of the atomization chamber and were diluted with chamber ventilation air to produce the desired exposure concentrations in the chambers.

Vapor Concentration Monitoring

The concentration of toluene in the chambers was measured in sampled chamber air at 3.3 μ by a MIRAN® gas-phase infrared spectrophotometer connected to a Hewlett-Packard Model 3388A laboratory computer. Air from each chamber was sampled and analyzed about 5 minutes every hour. Weekly mean exposure concentrations for the 14- and 15-week and 2-year studies are presented in Tables I2 and I3. Toluene aerosol, measured in the 1,200-ppm chamber with a Sibata® P-5 Digital Dust Indicator (2-year studies) or in the 3,000-ppm chamber with a Model CI-252 (Climet Instrument Co.) aerosol particle counter (14-week studies), was not detected in measurable quantitites.

The presence of detectable concentrations (more than 10 ppm) of toluene was determined by analyzing the atmosphere in all chambers postexposure at various times. Measurable concentrations occurred by 4 months after the studies began, and, after further evaluation, the animals and/or caging were indicated as the source of the residual toluene.

TABLE 12. MEAN CHAMBER CONCENTRATIONS IN THE FOURTEEN-WEEK AND FIFTEEN-WEEK INHALATION STUDIES OF TOLUENE

Week on Study	Weekly Chamber Concentration (ppm) (a)					
	0	100	625	1,250	2,500	3,000
1	5	89	697	584	1,859	3,123
2	2	99	641	732	2,113	3,282
3	7	89	548	600	2,383	2,677
4	1	93	601	913	2,246	2,940
5	1	81	604	1,120	2,116	2,757
6	8	95	605	1,182	2,353	2,992
7	12	97	624	1,276	2,458	2,878
8	16	105	659	1,200	2,592	2,923
9	15	107	688	1,208	2,398	2,980
10	20	95	627	1,205	2,432	2,941
11	22	88	596	1,094	2,323	2,848
12	21	90	562	1,087	2,584	2,865
13	27	91	577	1,113	2,316	2,788
14	25	95	577	1,110	2,366	2,932
(b) 15 (mice)	24	90	573	1,073	2,175	2,760
15 (rats)	23	85	565	1,026	2,175	2,760
(c) 16 (rats)	20	74	491	1,025	2,220	3,013

(a) Calculated as the mean of the actual hourly concentration
(b) One exposure during week 15
(c) One exposure during week 16

TABLE I3. MEAN CHAMBER CONCENTRATIONS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE

Week on Study: Rats	Week on Study: Mice	Weekly Mean Chamber Concentration (ppm): 0	120	600	1,200
1	--	0	--	614	1,211
2	--	0	--	581	1,167
3	--	0	--	563	1,173
4	--	1	--	573	1,136
5	--	0	--	624	1,188
6	--	0	--	621	1,214
7	1	1	122	621	1,210
8	2	1	124	618	1,144
9	3	0	118	576	1,230
10	4	1	118	577	1,137
11	5	0	120	614	1,183
12	6	0	124	617	1,144
13	7	1	120	618	1,158
14	8	0	110	580	1,203
15	9	0	115	582	1,093
16	10	1	104	570	1,046
17	11	2	114	559	1,166
18	12	2	113	563	1,186
19	13	1	115	525	1,215
20	14	0	117	520	1,202
21	15	1	121	499	1,156
22	16	1	131	614	1,214
23	17	3	122	595	1,178
24	18	8	124	628	1,194
25	19	0	118	597	1,207
26	20	0	121	616	1,226
27	21	0	120	579	1,187
28	22	0	118	598	1,214
29	23	0	123	592	1,200
30	24	0	123	583	1,230
31	25	1	119	588	1,205
32	26	1	117	580	1,186
33	27	0	122	584	1,217
34	28	0	118	591	1,185
35	29	0	124	620	1,171
36	30	0	124	599	1,149
37	31	0	123	612	1,117
38	32	0	128	618	1,134
39	33	0	119	612	1,103
40	34	4	123	609	1,135
41	35	0	121	633	1,165
42	36	2	120	634	1,219
43	37	5	118	604	1,233
44	38	1	125	599	1,246
45	39	1	118	601	1,167
46	40	0	120	585	1,192
47	41	1	120	603	1,195
48	42	0	123	600	1,248
49	43	1	121	598	1,177
50	44	2	123	624	1,290
51	45	3	112	598	1,158
52	46	0	112	549	1,177
53	47	1	118	593	1,230
54	48	2	115	565	1,183
55	49	0	117	596	1,179
56	50	1	111	620	1,159
57	51	7	114	615	1,167
58	52	2	119	582	1,094
59	53	6	122	609	1,164
60	54	8	114	610	1,156
61	55	10	118	596	1,130

TABLE I3. MEAN CHAMBER CONCENTRATIONS IN THE TWO-YEAR INHALATION STUDIES OF TOLUENE (Continued)

Week on Study		Weekly Mean Chamber Concentration (ppm)			
Rats	Mice	0	120	600	1,200
62	56	8	117	568	1,188
63	57	5	122	580	1,196
64	58	8	115	590	1,169
65	59	2	118	600	1,149
66	60	0	118	592	1,151
67	61	0	121	582	1,158
68	62	0	126	608	1,141
69	63	0	119	609	1,181
70	64	0	124	564	1,194
71	65	0	123	564	1,185
72	66	0	128	544	1,182
73	67	0	125	593	1,147
74	68	0	127	598	1,149
75	69	0	123	601	1,165
76	70	0	121	591	1,179
77	71	0	118	613	1,179
78	72	0	117	596	1,106
79	73	0	119	590	1,201
80	74	0	122	597	1,210
81	75	0	120	598	1,205
82	76	4	121	604	1,195
83	77	3	120	590	1,150
84	78	5	122	595	1,220
85	79	4	122	597	1,208
86	80	4	123	599	1,205
87	81	3	118	596	1,209
88	82	3	119	607	1,200
89	83	1	119	597	1,189
90	84	2	119	606	1,180
91	85	1	123	592	1,201
92	86	2	119	605	1,197
93	87	2	119	595	1,175
94	88	1	122	606	1,178
95	89	2	121	597	1,212
96	90	1	118	599	1,210
97	91	0	123	598	1,218
98	92	0	116	587	1,184
99	93	0	120	580	1,207
100	94	0	123	576	1,159
101	95	0	121	596	1,210
102	96	0	120	587	1,160
103	97	0	117	585	1,169
--	98	0	126	588	1,114
--	99	0	118	594	1,018
--	100	0	123	607	1,162
--	101	0	128	582	1,171
--	102	1	124	582	1,117
--	103	0	115	592	1,264

APPENDIX I. CHEMICAL CHARACTERIZATION

Vapor Concentration Uniformity in Chamber

The uniformity of the vapor concentration in each exposure chamber was measured at intervals over a 5-month period during the studies with the same system used to monitor the vapor concentration (used as a reference at the site normally used for analytical measurements during the studies) and a second system with a different infrared monitor used as a comparison with the reference. Between each hourly sample for the main analytical system (reference site), the probe on the second system was moved to predetermined test sites that encompassed the entire animal exposure zone; in four of the five tests that used this combined system, the range of variation from the reference was 3%-12%, whereas in the fifth test, it was 26% (77%-103% that of the reference). In the three tests that used only the second infrared monitor (used as both reference and comparison monitors by serially sampling the reference and six comparison sites, beginning and ending with the reference site), variations from the reference position were 2%, 5%, and 14%.

APPENDIX J

GENETIC TOXICOLOGY OF TOLUENE

APPENDIX J. GENETIC TOXICOLOGY

METHODS

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

Chemicals were tested in four strains; all trials were repeated. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 1 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

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

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

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

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

RESULTS

Toluene, within a dose range of 10-1,000 µg/plate, did not induce reverse gene mutations in four strains of *S. typhimurium* (TA98, TA100, TA1535, or TA1537) when tested in a preincubation protocol in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table J1). In the mouse lymphoma assay for induction of Tft resistance in L5178Y/TK cells, toluene was positive in trials conducted with and without Aroclor 1254-induced male F344 rat liver S9 (McGregor et al., 1988; Table J2); significant responses were noted at doses of 200 µg/ml and above, which, in all but one trial, represented the highest nonlethal dose tested. Despite the statistically positive, reproducible responses observed in this assay, the overall conclusion was judged to be equivocal because the presence of a toluene/water emulsion could not be ruled out conclusively, therefore leaving a question of whether acceptable dose levels had been achieved in this assay as per the study criteria set forth in McGregor et al. (1988). In cytogenetic tests with cultured CHO cells, toluene did not induce SCEs (Table J3) or chromosomal aberrations (Table J4) when tested with doses up to 1,600 µg/ml in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9; no induction of cell cycle delay, necessitating delayed harvest, was noted at any of the nonlethal doses tested.

TABLE J1. MUTAGENICITY OF TOLUENE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+10% S9 (hamster) Trial 1	+10% S9 (hamster) Trial 2	+10% S9 (rat) Trial 1	+10% S9 (rat) Trial 2
TA100	0	86 ± 6.8	99 ± 5.2	89 ± 5.5	104 ± 5.3	115 ± 8.7	92 ± 3.8	113 ± 2.0
	10	98 ± 11.2	88 ± 4.3	47 ± 3.8	85 ± 5.0	96 ± 6.0	88 ± 2.4	108 ± 2.5
	33.3	99 ± 12.7	110 ± 23.8	53 ± 1.8	99 ± 4.6	112 ± 4.5	90 ± 6.8	117 ± 12.5
	100	94 ± 7.5	167 ± 51.1	58 ± 3.2	102 ± 6.7	118 ± 15.6	84 ± 2.3	124 ± 5.5
	333.3	93 ± 4.2	226 ± 52.3	60 ± 4.7	94 ± 2.7	100 ± 1.9	96 ± 7.4	114 ± 18.3
	1,000	(c) 71 ± 2.1	(c) 90 ± 3.8	(c) 51 ± 3.2	86 ± 9.3	69 ± 10.8	103 ± 10.4	(c) 95 ± 14.2
Trial summary		Negative	Positive	Negative	Negative	Negative	Negative	Negative
Positive control (d)		519 ± 14.7	625 ± 28.8	494 ± 8.4	1,507 ± 41.2	963 ± 104.3	604 ± 39.5	460 ± 15.3

Strain	Dose (µg/plate)	-S9 Trial 1	-S9 Trial 2	+10% S9 (hamster) Trial 1	+10% S9 (hamster) Trial 2	+10% S9 (rat) Trial 1	+10% S9 (rat) Trial 2
TA1535	0	20 ± 2.6	20 ± 1.0	10 ± 0.3	13 ± 0.6	6 ± 1.3	13 ± 3.0
	10	24 ± 4.3	17 ± 0.6	12 ± 3.1	11 ± 2.7	9 ± 3.2	8 ± 2.0
	33.3	22 ± 3.9	22 ± 3.9	8 ± 0.9	11 ± 2.5	9 ± 2.0	10 ± 1.5
	100	16 ± 2.3	14 ± 2.2	10 ± 2.5	10 ± 1.2	10 ± 3.1	11 ± 1.5
	333.3	19 ± 4.4	21 ± 3.5	8 ± 2.6	12 ± 2.6	9 ± 1.5	8 ± 2.2
	1,000	(c) 12 ± 0.9	(c) 14 ± 1.7	11 ± 3.5	(c) 7 ± 0.9	8 ± 2.7	(c) 9 ± 1.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		512 ± 18.9	444 ± 23.0	374 ± 16.0	268 ± 34.8	389 ± 11.4	305 ± 3.2
TA1537	0	7 ± 1.0	8 ± 1.0	16 ± 2.2	12 ± 2.7	14 ± 1.2	14 ± 1.9
	10	7 ± 1.0	8 ± 0.9	19 ± 4.0	11 ± 1.9	16 ± 4.8	13 ± 2.0
	33.3	6 ± 0.3	8 ± 2.9	19 ± 1.2	12 ± 1.9	9 ± 3.0	14 ± 3.5
	100	10 ± 1.3	9 ± 3.0	20 ± 2.7	14 ± 3.2	7 ± 1.0	10 ± 1.2
	333.3	7 ± 1.0	9 ± 2.0	15 ± 1.5	18 ± 5.5	7 ± 1.2	11 ± 2.0
	1,000	7 ± 1.9	(c) 6 ± 2.3	17 ± 1.8	(c) 2 ± 1.0	5 ± 0.9	(c) 9 ± 2.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		227 ± 43.8	710 ± 64.7	556 ± 24.3	244 ± 5.8	365 ± 19.7	158 ± 10.6
TA98	0	17 ± 2.4	27 ± 3.1	25 ± 0.9	37 ± 4.7	27 ± 3.5	35 ± 2.3
	10	22 ± 3.0	28 ± 0.3	26 ± 5.9	33 ± 1.3	24 ± 1.8	35 ± 3.4
	33.3	21 ± 3.4	25 ± 0.3	29 ± 6.4	41 ± 1.8	23 ± 3.7	37 ± 2.9
	100	19 ± 5.2	24 ± 5.9	28 ± 0.7	34 ± 1.5	23 ± 3.8	28 ± 1.5
	333.3	22 ± 3.3	25 ± 3.4	26 ± 4.1	39 ± 4.1	17 ± 0.7	32 ± 4.7
	1,000	16 ± 0.7	(c) 19 ± 2.9	29 ± 1.5	(c) 20 ± 2.6	23 ± 2.2	(c) 29 ± 0.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		645 ± 7.4	636 ± 3.4	1,292 ± 27.6	1,258 ± 130.5	428 ± 24.2	288 ± 3.0

(a) Study performed at SRI International. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE J2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY TOLUENE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
−S9					
Trial 1					
Dimethyl sulfoxide (d)		65.0 ± 5.4	100.0 ± 14.8	120.8 ± 12.9	62.5 ± 4.7
Toluene	31.25	69.0 ± 3.0	74.5 ± 0.5	129.0 ± 18.0	62.0 ± 6.0
	62.5	59.5 ± 2.5	66.5 ± 0.5	122.0 ± 28.0	68.0 ± 13.0
	125	66.0 ± 3.0	91.0 ± 20.0	124.5 ± 7.5	63.0 ± 1.0
	250	66.5 ± 6.5	28.0 ± 0.0	228.0 ± 30.0	(e) 114.5 ± 3.5
	500	Lethal	--	--	--
Methyl methanesulfonate	15	37.5 ± 3.5	38.5 ± 9.5	446.5 ± 29.5	(e) 401.0 ± 14.0
Trial 2					
Dimethyl sulfoxide (d)		74.8 ± 1.3	100.3 ± 7.8	126.0 ± 15.0	56.3 ± 6.6
Toluene (f)	50	75.7 ± 9.8	104.3 ± 7.5	138.3 ± 10.9	61.7 ± 4.7
	100	75.7 ± 3.3	95.7 ± 9.7	130.7 ± 18.5	57.3 ± 6.8
	200	82.0 ± 11.5	60.3 ± 3.7	209.0 ± 22.9	(e) 86.7 ± 6.8
	300	Lethal	--	--	--
Methyl methanesulfonate	15	22.0 ± 2.0	13.5 ± 1.5	304.0 ± 17.0	(e) 462.5 ± 19.5
Trial 3					
Dimethyl sulfoxide (d)		67.8 ± 5.2	100.3 ± 4.8	119.3 ± 4.9	59.5 ± 3.4
Toluene	150	68.5 ± 11.5	66.5 ± 10.5	157.0 ± 20.0	77.0 ± 3.0
	175	70.0 ± 2.0	64.0 ± 11.0	168.0 ± 38.0	81.0 ± 21.0
	200	80.0 ± 4.0	41.0 ± 9.0	243.0 ± 33.0	(e) 103.0 ± 19.0
	225	62.5 ± 5.5	21.0 ± 5.0	347.5 ± 80.5	(e) 184.0 ± 27.0
	250	58.5 ± 5.5	13.5 ± 5.5	471.5 ± 76.5	(e) 274.5 ± 67.5
	275	Lethal	--	--	--
Methyl methanesulfonate	15	23.5 ± 3.5	16.5 ± 2.5	303.5 ± 48.5	(e) 428.0 ± 7.0
+S9 (g)					
Trial 1					
Dimethyl sulfoxide (d)		95.5 ± 8.2	100.0 ± 1.7	118.0 ± 3.9	41.8 ± 2.4
Toluene	6.25	91.0 ± 6.0	100.0 ± 8.0	130.0 ± 15.0	48.0 ± 9.0
	12.5	92.5 ± 3.5	107.0 ± 5.0	140.5 ± 13.5	50.5 ± 2.5
	25	84.0 ± 6.0	82.5 ± 4.5	127.0 ± 5.0	50.5 ± 1.5
	50	94.0 ± 17.0	98.5 ± 5.5	126.5 ± 15.5	45.5 ± 2.5
	100	88.0 ± 3.0	92.0 ± 9.0	123.0 ± 17.0	47.0 ± 8.0
	200	74.5 ± 3.5	40.5 ± 1.5	162.0 ± 12.0	(e) 72.5 ± 8.5
Methylcholanthrene	2.5	69.0 ± 10.0	83.5 ± 6.5	347.0 ± 15.0	(e) 169.5 ± 17.5

TABLE J2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY TOLUENE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
+S9 (Continued)					
Trial 2					
Dimethyl sulfoxide		63.0 ± 2.0	100.0 ± 4.0	128.5 ± 9.5	67.5 ± 2.5
Toluene	125	65.5 ± 0.5	76.5 ± 0.5	134.5 ± 16.5	68.5 ± 7.5
	150	62.0 ± 2.0	73.5 ± 2.5	127.0 ± 5.0	68.0 ± 0.0
	175	53.0 ± 3.0	58.5 ± 0.5	118.5 ± 12.5	75.0 ± 4.0
	200	47.5 ± 4.5	35.5 ± 1.5	137.5 ± 1.5	98.5 ± 8.5
	(h) 225	45.5 ± 4.5	18.0 ± 0.0	189.5 ± 27.5	(e) 138.0 ± 6.0
	250	Lethal	--	--	--
Methylcholanthrene	2.5	30.0 ± 3.0	27.0 ± 1.0	570.5 ± 22.5	(e) 635.0 ± 42.0

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate, unless otherwise indicated; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the results of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the results of three tests.
(g) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.
(h) Precipitation occurred at this concentration.

TABLE J3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY TOLUENE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,051	490	0.47	9.8	27.0	
Toluene	50	50	1,050	423	0.40	8.5	27.0	86.7
	160	50	1,045	492	0.47	9.8	27.0	100.0
	500	50	1,034	496	0.48	9.9	27.0	101.0
	1,600	0						
	5,000	0						
Mitomycin C	0	50	1,050	753	0.72	15.1	27.0	154.1
	0.01	10	210	572	2.72	57.2	27.0	583.7
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,052	436	0.41	8.7	26.5	
Toluene	100	50	1,047	460	0.44	9.2	26.5	105.7
	200	50	1,044	426	0.41	8.5	26.5	97.7
	300	50	1,038	474	0.46	9.5	26.5	109.2
	400	0						
	4,000	0						
	5,000	0						
Mitomycin C	0	50	1,047	632	0.60	12.6	26.0	144.8
	0.01	10	210	446	2.12	44.6	26.5	512.6
+S9 (d)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,051	436	0.41	8.7	26.5	
Toluene	16	50	1,046	433	0.41	8.7	26.5	100.0
	50	50	1,045	416	0.40	8.3	26.5	95.4
	160	50	1,045	457	0.44	9.1	26.5	104.6
	500	22	459	205	0.45	9.3	26.5	106.9
	1,600	0						
Cyclophosphamide	0.3	50	1,042	759	0.73	15.2	26.5	174.7
	2	10	211	480	2.27	48.0	26.5	551.7
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,044	413	0.4	8.3	26.0	
Toluene	50	50	1,044	396	0.38	7.9	26.0	95.2
	100	50	1,046	413	0.39	8.3	26.0	100.0
	250	50	1,049	413	0.39	8.3	26.0	100.0
	500	0						
Cyclophosphamide	0.3	50	1,050	605	0.58	12.1	26.0	145.8
	2	10	209	414	1.98	41.4	26.0	498.8

TABLE J3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY TOLUENE (Continued)

(a) Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE J4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY TOLUENE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 12 h					Harvest time: 13.3 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0	0.0		100	1	0.01	1.0
Toluene					Toluene				
50	100	1	0.01	1.0	50	100	3	0.03	3.0
160	100	2	0.02	2.1	60	100	2	0.02	2.0
500	100	1	0.01	1.0	500	100	1	0.01	1.0
1,600	100	3	0.03	3.0	1,600	100	4	0.04	4.0
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.125	100	5	0.05	5.0	15	100	10	0.10	10.0
0.25	100	27	0.27	19.0	50	50	28	0.56	48.0

(a) Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX K

AUDIT SUMMARY

APPENDIX K. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and the draft NTP Technical Report No. 371 for the 2-year studies of toluene in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, room and exposure-chamber environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, data entry discrepancies on necropsy record forms, and correlation between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper match, inventory, and preservation.
(8) All microscopic diagnoses for a random 20% sample of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, with the exception that some or all records for method of randomization, disposition of surplus animals and study chemical, frequency of feeding, frequency of rack changes and cleaning of inner chamber surfaces, room light cycle, last day of dosing for interim-kill animals, and chemical use log were not available at the Archives. Records documented that exposure concentrations were generated, monitored, and administered properly. Some body weight fluctuations possibly occurred when animal numbers and weight data were confused for 51/53 high dose male rats on one occasion (week 52) and entered into the computer, resulting in an apparent weight loss for these animals. Recalculation of approximately 10% of the group mean body weight values in the Technical Report showed 21/25 for rats and 22/24 for mice to be correct; differences ranged from 1.9% to 8.8%. All external masses observed inlife were correlated with masses noted at necropsy for both rats and mice. The disposition code and date of death recorded at necropsy for each unscheduled-death animal (185 rats and 73 mice) had matching entries in the inlife records, except for the dates of death for 2 mice, which had no effect on survival values given in the Technical Report.

Individual animal identifiers (ear tags for rats and toe clips for mice) were present and correct in the residual tissue bags for 62/69 rats and 59/70 mice examined. Review of the entire data trail for the 7 rats and 11 mice with less than complete and correct identifiers indicated that the integrity of their individual animal identity had been maintained, but the absence of ear tags and toe clips had not been documented. A total of five untrimmed potential lesions were found in the wet tissues of 69 rats examined and nine in the wet tissues of 70 mice; none involved target organs. Intestinal segments were not completely opened for 24/69 rats and 38/70 mice, and the stomach was partially opened in 13 rats; however, no potential lesions were evident by external examination. Gross observations made at necropsy were correlated with microscopic diagnoses. Tissue blocks and slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables.

Full details about these and other audit findings are presented in the audit reports that are on file at NIEHS. This summary describes the extent to which the data and factual information presented in the Technical Report for the 2-year inhalation studies of toluene are supported by the records at the NTP Archives.

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