NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF ETHYLBENZENE

(CAS NO. 100-41-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

January 1999

NTP TR 466

NIH Publication No. 99-3956

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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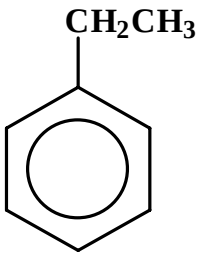
CONTENTS

ABSTRACT



ETHYLBENZENE

CAS No. 100-41-4

Chemical Formula: C_8H_{10} Molecular Weight: 106.16

Synonyms: EB; ethylbenzol; phenylethane

Ethylbenzene is mainly used in the manufacture of styrene. Ethylbenzene is also a major component of mixed xylenes used as solvents in agricultural and home insecticide sprays, rubber and chemical manufacturing, and household degreasers, paints, adhesives, and rust preventives. Ethylbenzene is also used as an antiknock agent in aviation and motor fuels. Ethylbenzene was nominated for study by the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) because of its potential for widespread human exposure and because of its structural similarity to benzene and toluene. Male and female F344/N rats and $B6C3F_1$ mice were exposed to ethylbenzene (greater than 99% pure) by inhalation for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes. In previously reported 13-week toxicity studies in which F344/N rats and $B6C3F_1$ mice were exposed to ethylbenzene by whole body inhalation exposure, no histopathologic changes were observed (NTP, 1992).

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation, 6 hours per day, 5 days per week, for 104 weeks.

Survival and Body Weights

Survival of male rats in the 750 ppm group was significantly less than that of the chamber controls. Mean body weights of 250 and 750 ppm males were generally less than those of the chamber controls beginning at week 20. Mean body weights of exposed groups of females were generally less than those of chamber controls during the second year of the study.

Pathology Findings

In male rats exposed to 750 ppm, the incidences of renal tubule adenoma and adenoma or carcinoma (combined) were significantly greater than the chamber control incidences. In addition, the incidence of renal tubule hyperplasia in 750 ppm males was significantly greater than that in the chamber controls.

The findings from an extended evaluation (step section) of the kidneys showed a significant increase in the incidences of renal tubule adenoma and hyperplasia in 750 ppm males and females; the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased in 750 ppm males. The severities of nephropathy in 750 ppm male and all exposed female rats were significantly increased relative to the chamber controls.

The incidence of interstitial cell adenoma in the testis of 750 ppm males was significantly greater than that in the chamber control group and slightly exceeded the historical control range for inhalation studies.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation, 6 hours per day, 5 days per week, for 103 weeks.

Survival and Body Weights

Survival of exposed groups of male and female mice was similar to that of the chamber controls. Mean body weights of female mice exposed to 75 ppm were greater than those of the chamber controls from week 72 until the end of the study.

Pathology Findings

In 750 ppm males, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater than those in the chamber control group but were within the NTP historical control ranges. The incidence of alveolar epithelial metaplasia in 750 ppm males was significantly greater than that in the chamber controls.

In 750 ppm females, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly greater than those in the chamber control group but were within the historical control ranges. The incidence of eosinophilic foci in 750 ppm females was significantly increased compared to that in the chamber controls. There was a spectrum of nonneoplastic liver changes related to ethylbenzene exposure in male mice, including syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis.

The incidences of hyperplasia of the pituitary gland pars distalis in 250 and 750 ppm females and the incidences of thyroid gland follicular cell hyperplasia in 750 ppm males and females were significantly increased compared to those in the chamber control groups.

GENETIC TOXICOLOGY

Ethylbenzene gave little indication of mutagenicity, *in vitro* or *in vivo*. No induction of mutations was noted in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535 with or without S9 metabolic activation, and no increases in sister chromatid exchanges or chromosomal aberrations were observed in cultured Chinese hamster ovary cells treated with ethylbenzene, with or without S9. In the mouse lymphoma assay, a significant mutagenic response was noted in the absence of S9, but only at the highest nonlethal dose tested and with accompanying cytotoxicity; the test was not performed with S9. No increases in the frequency of micronucleated erythrocytes were observed *in vivo* in peripheral blood samples from male and female mice exposed to ethylbenzene for 13 weeks.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of ethylbenzene in male F344/N rats based on increased incidences of renal tubule neoplasms. The incidences of testicular adenoma were also increased. There was *some evidence of carcinogenic activity* of ethylbenzene in female F344/N rats based on increased incidences of renal tubule adenomas. There was *some evidence of carcinogenic activity* of ethylbenzene in male B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *some evidence of carcinogenic activity* of ethylbenzene in female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms.

Exposure of male and female rats to ethylbenzene resulted in increased incidences of renal tubule

hyperplasia and increased severities of nephropathy. Exposure of male mice to ethylbenzene resulted in increased incidences of alveolar epithelial metaplasia, syncytial alteration of hepatocytes, hepatocellular hypertrophy, hepatocyte necrosis, and thyroid gland follicular cell hyperplasia. In female mice, ethylbenzene exposure resulted in increased incidences of eosinophilic foci of the liver, pituitary gland pars distalis hyperplasia, and thyroid gland follicular cell hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Ethylbenzene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 75, 250, or 750 ppm	Chamber control, 75, 250, or 750 ppm	Chamber control, 75, 250, or 750 ppm	Chamber control, 75, 250, or 750 ppm
Body weights	250 and 750 ppm groups less than chamber controls	Exposed groups less than chamber controls	Exposed groups similar to chamber controls	75 ppm group greater than chamber controls
Survival rates	15/50, 14/50, 13/50, 2/50	31/50, 31/50, 34/50, 35/49	28/50, 36/50, 32/50, 30/50	35/50, 38/50, 40/50, 37/50
Nonneoplastic effects	Kidney: renal tubule hyperplasia (standard evaluation - 2/50, 2/50, 4/50, 12/50; standard and extended evaluations combined - 11/50, 9/50, 11/50, 23/50); severity of nephropathy (2.3, 2.4, 2.3, 3.5)	Kidney: renal tubule hyperplasia (standard evaluation - 0/50, 1/50, 3/50, 3/49; standard and extended evaluations combined - 1/50, 2/50, 4/50, 10/49); severity of nephropathy (1.3, 1.6, 1.7, 2.3)	Lung: alveolar epithelial metaplasia (0/50, 1/50, 2/50, 6/50) Liver: syncytial alteration (0/50, 5/50, 8/50, 23/50); hypertrophy (1/50, 0/50, 0/50, 17/50); necrosis (1/50, 1/50, 3/50, 10/50) Thyroid gland: follicular cell hyperplasia (21/50, 21/50, 29/50, 32/50)	Liver: eosinophilic focus (5/50, 7/50, 6/50, 22/50) Pituitary gland (pars distalis): hyperplasia (10/48, 12/49, 23/47, 22/49) Thyroid gland: follicular cell hyperplasia (18/50, 23/50, 25/50, 35/50)
Neoplastic effects	Kidney: renal tubule adenoma (standard evaluation - 0/50, 3/50, 2/50, 4/50; standard and extended evaluations combined - 3/50, 5/50, 7/50, 20/50); renal tubule adenoma or carcinoma (standard evaluation - 0/50, 3/50, 3/50, 7/50; standard and extended evaluations combined - 3/50, 5/50, 8/50, 21/50) Testes: adenoma (36/50, 33/50, 40/50, 44/50)	Kidney: renal tubule adenoma (standard evaluation - 0/50, 0/50, 0/50, 1/49; standard and extended evaluations combined - 0/50, 0/50, 1/50, 8/49)	Lung: alveolar/ bronchiolar adenoma (5/50, 9/50, 10/50, 16/50); alveolar/ bronchiolar adenoma or carcinoma (7/50, 10/50, 15/50, 19/50)	Liver: hepatocellular adenoma (6/50, 9/50, 12/50, 16/50); hepatocellular adenoma or carcinoma (13/50, 12/50, 15/50, 25/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Ethylbenzene (continued)

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Level of evidence of carcinogenic activity	Clear evidence	Some evidence	Some evidence	Some evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:			Negative in strains TA97, TA98, TA100, and TA1535 with and without S9	
Mouse lymphoma gene mutations:			Positive without S9	
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:			Negative with and without S9	
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:			Negative with and without S9	
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:			Negative	

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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report 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 five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to 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 chemical-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 chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-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. Such consideration 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:

- 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 incidence 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);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- 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.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on ethylbenzene on 11 and 12 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 and 12 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of ethylbenzene received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. P.C. Chan, NIEHS, introduced the toxicology and carcinogenesis studies of ethylbenzene by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions were *clear evidence of carcinogenic activity* in male F344/N rats and *some evidence of carcinogenic activity* in female F344/N rats and male and female $B6C3F_1$ mice.

Dr. Reddy, a principal reviewer, agreed with the proposed conclusions. He said that for the purpose of contrasting findings with those of Maltoni *et al*. (1985), the Technical Report should cite information on types, sites, and incidences of neoplasms from that study. Dr. Chan said that in that study, the total number of neoplasms was provided but not differentiated by target organ. Dr. Reddy noted that the methods, such as immunochemistry, used to rule out α2µ-globulin nephropathy in male rats should be described in the Technical Report. Dr. J. Mahler, NIEHS, responded that the hematoxylin-eosin stain, a good screen for hyaline droplet accumulation, was used.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions for rats and female mice. He agreed that the inhalation route was appropriate, but he noted that ethylbenzene has been detected in surface and ground water. Dr. Goldsworthy thought that the additional information obtained from renal step sections was helpful but asked for justification of the decision to step section kidneys but not other organs, such as thyroid and pituitary glands. Dr. J.R. Hailey, NIEHS, said that the major reason to step section organs is to help interpret equivocal or uncertain effects, and that endocrine organs such as thyroid and pituitary glands are too small to step section. Dr. Goldsworthy suggested that *clear evidence of carcinogenic activity* may have been a better call in male mice, based on a positive exposure-response trend and the presence of metaplasia in the target tissue. Dr. Mahler said that metaplasia is an unusual lesion and is generally not recognized as a precursor to neoplasia.

Dr. Ryan, the third principal reviewer, agreed with the proposed conclusions for rats. She said that one of the reasons for studying the chemical was its structural similarity to benzene and toluene, and she questioned why the Technical Report did not include more discussion comparing the toxic effects of the three chemicals (see Table 12, page 49). She expressed concern that the 750 ppm exposure in female rats and in male and female mice may have been too low because there were no survival or body weight effects in these groups. Dr. J.R. Bucher, NIEHS, commented that prechronic studies were performed with ethylbenzene and that an NTP study report was published in 1992. Because there were essentially no histopathologic findings in the 13-week studies, the exposure selection for the 2-year study was based on a body weight deficit in male rats. Dr. Ryan said that it could be argued that there was *clear evidence of carcinogenic activity* in male mice based on an exposure-related increase in combined benign and malignant lung neoplasms and in female mice based on an exposure-related increase of combined benign and malignant hepatic neoplasms. Dr. J.K. Haseman, NIEHS, said that there were three reasons for the level of evidence chosen: first, the neoplasm rates fell within the historical control range; second, the neoplasms were primarily benign; and third, the lung neoplasms were seen only in males and the liver neoplasms only in females.

Dr. LeBoeuf commented that survival in 750 ppm male rats was only 4% but the level of evidence of carcinogenic activity in male rats was based on increased incidences of renal tubule neoplasms in the 750 ppm group. He said that he was uncomfortable

basing the level of evidence of carcinogenic activity on findings accompanied by such poor survival. Dr. Bucher responded that the fact that increased renal neoplasms were seen in both males and females and were accompanied by severe nephropathy, which is rarely if ever seen in females, suggests an intrinsic carcinogenic activity of ethylbenzene.

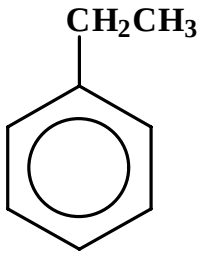
Dr. Ryan moved that the Technical Report on ethylbenzene be accepted with the revisions discussed and the conclusions as written for male rats, *clear evidence of carcinogenic activity*, and for female rats and male and female mice, *some evidence of carcinogenic activity*. Dr. Reddy seconded the motion, which was accepted unanimously with nine votes.

Later in the meeting, Dr. LeBoeuf made a motion to reopen the discussion on the neoplasm response in male rats. Dr. Taylor thought that the maker and seconder of the original motion should have to agree. Drs. Ryan and Reddy agreed to reopen the discussion. Dr. Goldsworthy seconded the motion to reopen the discussion, which was accepted by six yes votes to two no votes (Drs. Brown and Reddy). Dr. Ward was not present.

Dr. LeBoeuf stated that his primary concerns were the mortality in 750 ppm male rats and the interpretation of the data at that dose. He said that one of the original National Cancer Institute guidelines for the 2-year bioassays is that particular treatments should not affect survival, unless reduced survival is a result of neoplasia, and should not cause more than a 10% decrease in body weight gain. He said that in the ethylbenzene Technical Report, it was clear that the majority of the neoplasms in male rats were considered to be incidental to the cause of death. For this reason, he recommended changing the conclusion in male rats to *some evidence of carcinogenic activity*. Dr. Haseman pointed out that at week 84, the survival in 750 ppm male rats was still 70%. Dr. Goldsworthy stated that one issue to consider is when the first neoplasms arose. Dr. Bucher commented that nephropathy was likely the primary contributor to mortality. Dr. Haseman suggested that the conclusion for male rats, as with the report on oxazepam, could indicate that there was *clear evidence of carcinogenic activity* only at concentrations resulting in enhanced nephropathy. Dr. Bucher noted that in many past studies, the conclusions for carcinogenic activity were confirmed even when the maximum tolerated doses were exceeded. He noted that in most studies in which renal tubule neoplasms are associated with nephropathy in male rats, carcinomas are generally not seen; he further noted that in female rats, the incidences of nephropathy are generally less than in male rats and that 21 neoplasms is exceptionally high. Dr. Goldsworthy reminded the reviewers of the stipulation "Under the conditions of these studies…" Dr. Ryan pointed out that in the standard evaluation, the renal tubule neoplasm incidences in male rats exceeded the historical control range even in the 75 ppm group.

Dr. LeBoeuf moved that the conclusion for male rats be changed to *some evidence of carcinogenic activity*. Dr. Ryan seconded the motion, which was defeated by six no votes to two yes votes (Drs. LeBoeuf and Russo). Dr. Ward was not present.

INTRODUCTION



ETHYLBENZENE

CAS No. 100-41-4

Chemical Formula: C_8H_{10} Molecular Weight: 106.16

Synonyms: EB; ethylbenzol; phenylethane

CHEMICAL AND PHYSICAL PROPERTIES

Ethylbenzene is a colorless, flammable, aromatic liquid with a melting point of -95.0° C, a boiling point of 136.2° C at 760 mm Hg, and a density of 0.866 at 25° C. Its vapor pressure is 10 mm Hg at 25.9° C, and its vapor density is 3.66. It is practically insoluble in water (0.014 g/100 mL) at 15° C but is soluble in most organic solvents (Verschueren, 1983; *Merck Index*, 1989). Ethylbenzene has a flash point of 15° C and an autoignition temperature of 432° C (Lewis, 1992).

PRODUCTION, USE, AND HUMAN EXPOSURE

Ethylbenzene is produced by two primary processes: heating of benzene and ethylene in the presence of aluminum chloride and by fractionation directly from the mixed xylene stream during petroleum refining *(Hawley's*, 1987). The United States production of ethylbenzene was 7.56 billion pounds in 1984 (USITC, 1985), 8.5 billion pounds in 1986 (Heylin, 1987), 11.11 billion pounds in 1992, and 11.76 billion pounds in 1993 (*Chem. Eng. News*, 1994). Ethylbenzene was the eighteenth highest in production volume for chemicals produced in the United States in 1985 (*Hawley's*, 1987). Ethylbenzene is mainly used in the manufacture of styrene (*Fed. Regist.*, 1987) and cellulose acetate (ILO, 1983). It has also been used as an intermediate in the production of diethylbenzene, acetophenone, and ethyl anthraquinone. Ethylbenzene is a major component (15% to 20%) of mixed xylenes (Toftgard and Nilsen, 1982), which are used as solvents in agricultural and household insecticide sprays, rubber and chemical manufacturing industries, and household degreasing cleaners, paint, adhesives, and rust preventives (Fishbein, 1985). The United States produced 6.49 billion pounds of mixed xylenes in 1984 (USITC, 1985). Ethylbenzene has also been used in motor and aviation fuels as an antiknock agent (NIOSH, 1979; ILO, 1983).

Ethylbenzene is widely distributed in the environment due to its use as a solvent and fuel additive; it is also naturally present in crude petroleum. It has been detected in ambient air, surface water and groundwater, and in human milk (National Research Council, 1981). Ethylbenzene concentrations of 10 to 26 mg/L have been detected in the Missouri River (STORET, 1986) and concentrations up to 7 mg/L have been found in samples of potable water in Canada (Otson *et al.*, 1982). Ethylbenzene has also been found in wastewater effluents from pulpwood

mills (Nestmann *et al.*, 1980). Ethylbenzene was in a water sample from New Jersey, in eight air samples, and in 12 breath samples from workers exposed to ethylbenzene (Wallace *et al.*, 1984). Atmospheric air samples collected in the Los Angeles basin contained ethylbenzene, probably derived from vehicle exhaust (Lonneman *et al.*, 1968). No evidence of ethylbenzene bioaccumulation has been reported.

Based on irritant properties of ethylbenzene vapor, the American Conference of Governmental Industrial Hygienists (ACGIH, 1996) has set a threshold limit value of 100 ppm (435 mg/m^3), with a short-term exposure limit of 125 ppm (545 mg/m^3). The Occupational Safety and Health Administration (OSHA) set the permissible exposure limit at 100 ppm as an 8-hour time-weighted average and 125 ppm as a 15-minute short-term exposure limit (*Fed. Regist.*, 1989).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Structurally, ethylbenzene is related to other aliphatic derivatives of aromatic compounds. Many of the biological activities of these chemicals are similar. For example, benzene, ethylbenzene, and toluene are well absorbed after inhalation exposure and are distributed to adipose tissue, liver, kidney, bone marrow, and nervous tissue. These chemicals are metabolized mainly by the hepatic cytochrome P_{450} systems and are central nervous system depressants (Tegeris and Balster, 1994). The toxic effect on the central nervous system, at least in part, is exerted by inhibiting the membrane-bound ATPase activities in astrocytes (Naskali *et al.*, 1994; Vaalavirta and Tähti, 1995), thereby disturbing the ATPase-dependent astrocytic regulatory functions.

Toluene is metabolized by the liver cytochrome P_{450} enzyme system to benzyl alcohol, benzaldehyde, and benzoic acid via methyl hydroxylation and is excreted in the urine as hippuric acid. A minor pathway of metabolism is via ring hydroxylation and excretion as cresol sulphates and glucuronides (Dean, 1978). In NTP (1990a) inhalation studies, toluene was neither genotoxic nor carcinogenic. Ono *et al.* (1995) did not find toluene to be teratogenic in inhalation studies.

Benzene is metabolized primarily by the hepatic cytochrome P_{450} system to benzene oxide and then rearranged to form phenol, catechol, and benzoquinones (hydroquinones) and excreted in the urine or exhaled (NTP, 1986). Alternatively, oxidation and ring opening of catechol give rise to *trans,trans*-muconaldehyde and muconic acid. Hydration of benzene oxide to dihydrodiol and ring oxidation to diolepoxide have also been postulated (Busby *et al.*, 1990). Inhalation exposure to benzene in BDF_1 mice caused DNA damage in peripheral blood cells, bone marrow, and liver (Plappert *et al.*, 1994). The hematotoxicity of benzene observed in rats and mice is mainly due to the metabolites hydroquinone and benzoquinone (Zhu *et al.*, 1995). Xylene undergoes oxidation of the methyl group to give rise to methyl benzyl alcohols or aromatic hydroxylation to xylenols before excretion in the urine (Dean, 1978).

Percutaneous absorption rates of benzene, toluene, ethylbenzene, and aniline in male HRS/J hairless mice following an application of 5 mL of ^{14}C-labeled test solution were 56, 49, 37, and 2.3 µg/cm^2 per minute, respectively (Susten *et al.*, 1990). The excretion of benzene and aniline in expired air was greater during the first 15 minutes of exposure, whereas that of toluene and ethylbenzene was greatest during the second 15 minutes of exposure. These data suggested a two-compartment model might better describe the kinetics of the appearance of toluene and ethylbenzene in expired breath.

Differences in the metabolism of ethylbenzene in rats, rabbits, and humans are minor (Chin *et al.*, 1980; Climie *et al.*, 1983). Ethylbenzene metabolism appears to involve side-chain hydroxylation by liver microsomal enzymes (Pyykko *et al.*, 1987). Ring oxidation may also occur (Engström, 1984).

Experimental Animals

Ethylbenzene is readily absorbed from the atmosphere in Harlan-Wistar rats. In rats exposed to radiolabeled ethylbenzene for 6 hours by inhalation, radioactivity was found in the liver, gastrointestinal tract, and adipose tissue 42 hours after exposure (Chin *et al.*, 1980). One day following oral administration of radioactive ethylbenzene, radioactivity was found in the intestine, liver, kidney, and fat of rats (Climie

et al., 1983). Freundt *et al.* (1989) reported that the blood concentration of ethylbenzene was dose-dependent after a 2-hour inhalation of 120, 240, 350, or 650 ppm in rats.

In rats, ethylbenzene is metabolized to mandelic acid and phenylglyoxylic acid by side-chain oxidation and then excreted in the urine (Bardodej and Bardodejova, 1970; Engström, 1984; Gromiec and Piotrowski, 1984). Other minor metabolites found in urine included 1-phenylethanol, omega-hydroxyacetophenone, hippuric acid, benzoic acid, phenylacetic acid, and phenaceturic acid (Engström, 1984; Engström *et al.*, 1985). Engström (1984) showed that in male Wistar rats exposed to ethylbenzene by inhalation for 6 hours per day, 5 days per week, for 3, 5, and 9 weeks at 50, 300, or 600 ppm, the total urinary elimination of ethylbenzene metabolites in 24 hours was dose dependent. Excretion of metabolites into urine increased in a dose-related manner but less than linearly. The total amount of metabolites excreted at each time point at each dose was constant. These data implied induction of a metabolic enzyme.

Humans

Human exposure to ethylbenzene is mainly via inhalation of vapor and/or mist. To a smaller extent, absorption also occurs through dermal contact or by ingestion (Dutkiewicz and Tyras, 1967). Ethylbenzene is readily absorbed from the atmosphere through the lungs in humans (Bardodej and Bardodejova, 1970; Gromiec and Piotrowski, 1984), and orally administered ethylbenzene is quickly and effectively absorbed as well (Climie *et al.*, 1983). Absorption of liquid ethylbenzene through the skin is rapid when compared to similar hydrocarbon compounds such as benzene or styrene (Dutkiewicz and Tyras, 1967). Trace amounts of ethylbenzene were found in the subcutaneous fat (Wolf *et al.*, 1977) and body fat (Engström and Bjurstrom, 1978) of humans exposed to the chemical either by the dermal or inhalation route.

In humans, as in rats, most of the absorbed ethylbenzene is metabolized by liver microsomal enzymes to mandelic acid and phenylglyoxylic acid by side-chain oxidation and then excreted in the urine (Bardodej and Bardodejova, 1970; Engström, 1984; Gromiec and Piotrowski, 1984). However, a small amount of phenolic derivatives (2- and 4-ethylphenol) is also found in the urine (Angerer and Lehnert, 1979; Engström, 1984), indicating the occurrence of ring oxidation. The presence of phenaceturic acid in urine implies oxidation of the ω-methyl group of the side chain (Figure 1; Engström, 1984).

TOXICITY

Experimental Animals

The oral LD_{50} for ethylbenzene in male and female Wistar rats was estimated to be 3.5 g/kg (Wolf *et al.*, 1956), and the intraperitoneal LD_{50} for mice was 2.27 g/kg (DFG, 1985; Lewis, 1992). The 4-hour LC_{50} in female rats was 4,000 ppm, and the 1-hour LC_{50} was 8,000 ppm (Smyth *et al.*, 1962).

Ethylbenzene is a mucous membrane irritant; guinea pigs exposed for 1 minute to 0.2% ethylbenzene vapor experienced moderate eye and nasal irritation. Exposure to 0.1% ethylbenzene produced slight nasal irritation that ceased after 30 minutes. At 1%, ethylbenzene caused ataxia, loss of consciousness, tremor (Lewis, 1992), central nervous system depression, and death (ACGIH, 1986).

In Wistar rats, oral administration of ethylbenzene at 408 or 680 mg/kg per day or inhalation exposure at 1,250 or 2,200 ppm, 7 to 8 hours per day, 5 days per week for 6 months induced slight increases in kidney and liver weights and cloudy swelling of the tubular epithelium of the kidney and parenchymal cells of the liver (Wolf *et al.*, 1956). Male Wistar rats exposed to ethylbenzene by inhalation at 300 or 600 ppm for 16 weeks exhibited increased activities of liver enzymes, including NADPH cytochrome c reductase, 7-ethoxycoumarin-*O*-deethylase, UDP-glucuronosyltransferase, and D-glucuronolactone dehydrogenase. Kidney 7-ethoxycoumarin-*O*-deethylase and UDP-glucuronosyl-transferase activities were also increased (Elovaara *et al.*, 1985). Electron microscopy showed that the cloudy swelling of the renal tubule epithelium was due to an increase in endoplasmic reticulum as a result of an adaptive response of increased microsomal enzyme activity (Elovaara *et al.*, 1985). Rats exposed to ethylbenzene at 2,000 ppm for 3 days had increased hepatic cytochrome P_{450} and NADPH cytochrome c reductase activities (Toftgard and Nilsen, 1982). F344/N rats and $B6C3F_1$ mice

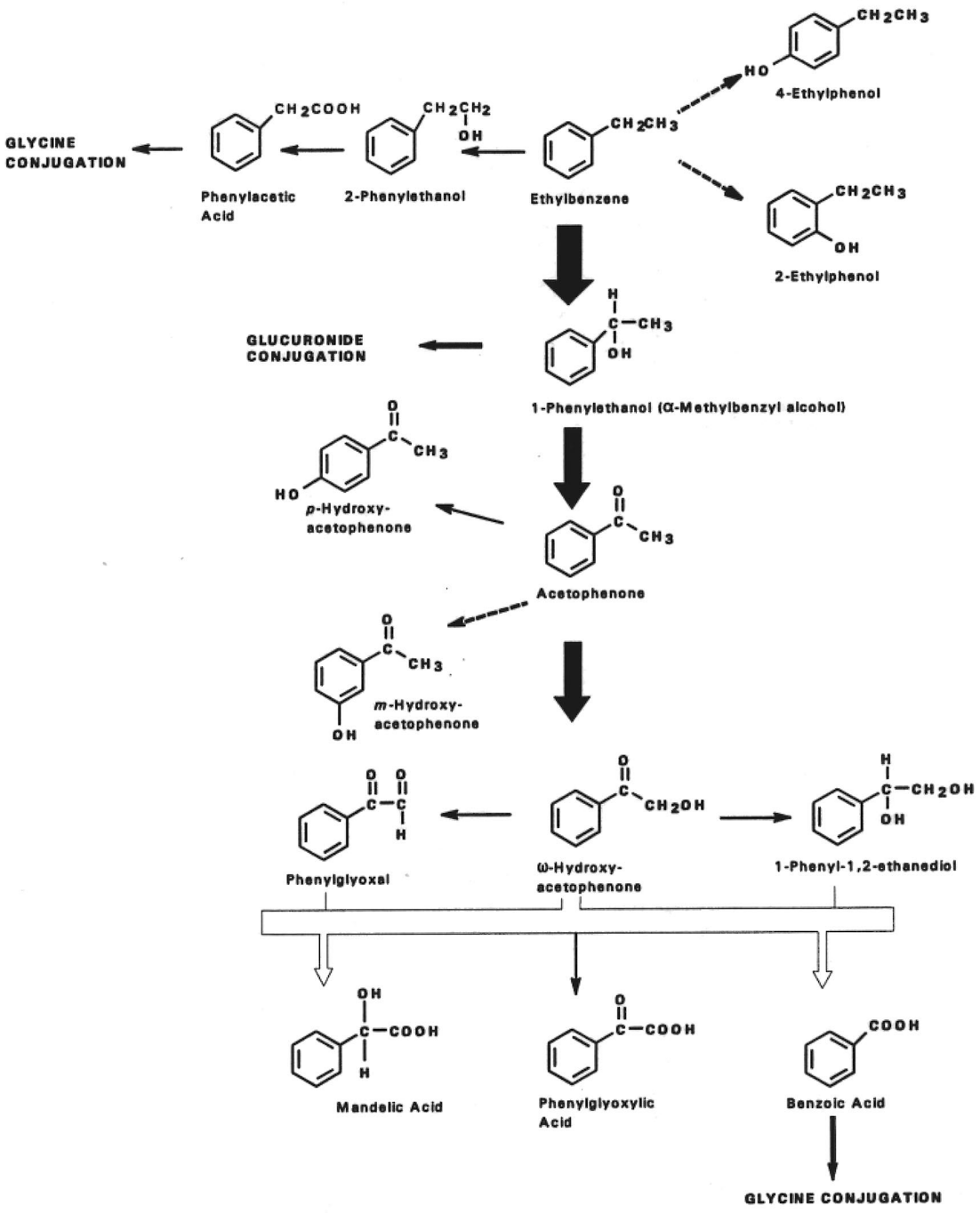


FIGURE 1
Metabolism of ethylbenzene as reconstructed from urinary metabolites found in rat and human urine. The thickness of the arrows represents the extent of the respective route; the broken arrows indicate that only trace amounts were found. Unclear pathways are depicted by open arrows (Reproduced from Engström, 1984).

exposed to ethylbenzene by inhalation at 382 or 782 ppm 5 days per week for 4 weeks had significantly increased absolute and relative liver weights (Cragg *et al.*, 1989). The authors concluded that the no-observed-adverse-effect-level for rats and mice was 382 ppm.

In 13-week toxicity studies performed by the NTP (1992), F344/N rats and B6C3F$_1$ mice were exposed to ethylbenzene by inhalation at 0, 100, 250, 500, 750, or 1,000 ppm. Signs of toxicity included increased liver, lung, and kidney weights in exposed male and female rats and increased liver weights in exposed male and female mice. No evidence of histopathologic injury was noted in these studies. No animals died, and the mean body weight gains of the exposed rats and mice did not differ from those of the respective controls. Sperm or vaginal cytology evaluations of the exposed rats and mice revealed no changes from normal. Based on the changes in organ weights, the high dose selected for the 2-year studies was 750 ppm.

Humans

Ethylbenzene is a skin, eye, and respiratory irritant and a central nervous system depressant at an atmospheric concentration of 0.2%. Human volunteers breathing 0.1% ethylbenzene vapor reported initial eye irritation which gradually decreased, while exposure to a 0.2% atmospheric concentration was accompanied by extreme irritation of the eyes, nose, and throat (Yant *et al.*, 1930) and central nervous system depression. Symptoms of central nervous system depression included headache; nausea; weakness; dizziness; sleepiness; loss of coordination, judgment, and consciousness; and coma or death (Lewis, 1992). Erythema and inflammation of the skin developed after dermal contact (Lewis, 1992). Prolonged exposure to ethylbenzene vapor may result in leukopenia and lymphocytosis, neurofunctional disorder, and hepatitis (ILO, 1983).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylbenzene is embryotoxic and teratogenic. The offspring of rats exposed to ethylbenzene at 1,000 ppm, 7 hours per day, 5 days per week for 3 weeks before mating, then exposed daily through day 19 of gestation had a higher incidence of supernumerary ribs (Hardin *et al.*, 1981). In the offspring of CFY rats exposed to ethylbenzene at 552 ppm, 24 hours per day from days 7 to 15 of gestation, retardation of skeletal development, increased incidence of supernumerary ribs, and anomalies of the uropoietic apparatus were observed (Ungvary and Tatrai, 1985). An increased rate of malformation was also found in CFLP mice exposed to ethylbenzene. Maternal toxicity reported by these investigators included increased liver, kidney, and spleen weights. Increased postimplantation loss of fetuses in dams was also observed.

CARCINOGENICITY

Maltoni *et al.* (1985) reported a study in which Sprague-Dawley rats were administered 500 mg ethylbenzene/kg per day in olive oil by gavage, 4 or 5 days per week for 104 weeks. Incidences of malignant neoplasms were 35.0% (versus 26.7% in controls) in dosed males and 45.9% (versus 22.4% in controls) in dosed females. The results of this study were considered inconclusive. No other information on the carcinogenicity of ethylbenzene in experimental animals or humans was found in the literature. Benzene, a homologue of ethylbenzene, is carcinogenic in rats and mice (NTP, 1986; Farris *et al.*, 1993) and is a human carcinogen inducing acute myelogenous leukemia and aplastic anemia.

GENETIC TOXICITY

Ethylbenzene was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535 when tested up to toxic doses (1,000 µg/plate) in the presence or absence of exogenous metabolic activation (S9) (Zeiger *et al.*, 1992). It was also reported to be negative, with and without S9, in *S. typhimurium* strains TA1537 and TA1538 (Nestmann *et al.*, 1980), in *Escherichia coli* WP2 and WP2uvrA, and in *Saccharomyces cerevisiae* JD1 (Dean *et al.*, 1985). A weakly positive response was reported in a sister chromatid exchange test with human lymphocytes cultured in the presence of S9 (Norppa and Vainio, 1983), and an increase in mutant L5178Y mouse lymphoma cell colonies was observed at the highest nonlethal dose (80 µg/mL) of ethylbenzene tested in the absence of S9 (McGregor *et al.*, 1988). Micronucleus assays in mouse peripheral blood were negative (NTP, 1992; Appendix E).

STUDY RATIONALE

Ethylbenzene was nominated for toxicity study by OSHA and NIOSH and was selected for study by the NTP because of its potential for widespread consumer exposure and its structural similarity to benzene and toluene. The present studies were undertaken following the designation of ethylbenzene as a priority chemical for toxicologic testing by the Interagency Agreement (Superfund) between the NTP and the United States Environmental Protection Agency (EPA). The studies were designed to determine the toxicologic and carcinogenic effects of ethylbenzene in F344/N rats and $B6C3F_1$ mice after a 2-year inhalation exposure. Data were needed for the EPA to make regulatory decisions mandated by the Clean Air Act (42 U.S.C. § 7412). The inhalation route of exposure was selected because human exposure to ethylbenzene is mainly by inhalation.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ETHYLBENZENE

Ethylbenzene was obtained from ARCO Chemical Company (Newtown Square, PA) in two lots (A060989 and A051890). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the ethylbenzene studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a clear, colorless, pungent smelling, volatile liquid, was identified as ethylbenzene by infrared, ultraviolet/visible (lot A060989 only), and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra of ethylbenzene. The boiling point and density of the chemical were also consistent with literature references.

The purity of lot A060989 was determined by elemental analyses, Karl Fischer water analysis, iodometric titration for peroxide determination, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for ethylbenzene. Karl Fischer water analysis indicated less than 0.05% water. Iodometric titration revealed no peroxide. Gas chromatography by two systems revealed a major peak and no impurities with areas greater than 0.1% relative to the major peak. Major peak comparisons of lot A060989 with a previously analyzed lot of ethylbenzene (lot K061786) not used in the current studies indicated a purity of 101.0% ± 0.5% for lot A060989 relative to lot K061786. The overall purity of lot A060989 was determined to be greater than 99%.

Additional analyses of lot A060989 were performed with gas chromatography/mass spectrometry to identify and quantify cumene in the bulk ethylbenzene. In these analyses, 62 ± 3.1 ppm cumene was detected.

The purity of lot A051890 was determined by iodometric titration for peroxide and by gas chromatography. Less than 2 ppm peroxide was detected. Gas chromatography indicated one impurity with an area of 0.1% relative to the major peak. The overall purity of lot A051890 was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. These studies indicated that ethylbenzene is stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in the original steel containers until just prior to use, when it was transferred to amber glass bottles with Teflon®-lined caps and a nitrogen headspace. The rapid use and small shipment sizes of ethylbenzene made stability monitoring unnecessary during the studies; however, the peroxide content of the bulk chemical was tested monthly with iodometric titration. The concentration of peroxide ranged from 1.12 to 10.7 ppm.

VAPOR GENERATION AND EXPOSURE SYSTEM

Ethylbenzene vapor was produced by flash evaporator units. Nitrogen gas carried ethylbenzene vapor from the condensing column into heated stainless-steel transfer lines that led to exposure chambers. Each exposure chamber was supplied by a separate flash evaporator unit. Exposure concentrations for individual exposure chambers were created by varying the ethylbenzene flow rate to the individual flash evaporation units. At the chamber inlets, the ethylbenzene vapor was mixed with HEPA- and charcoal-filtered air. Stainless-steel chambers (Hazleton H-2000®) manufactured by Lab Products, Inc. (Maywood, NJ) were used throughout the studies. The 750 ppm chambers were sampled once during the first full week of exposure for the presence of aerosol by a Quartz Crystal Microbalance Cascade Impactor

(California Measurements, Sierra Madre, CA). Results indicated that aerosol formation due to test atmosphere generation was not significant.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of ethylbenzene were monitored by an on-line gas chromatograph using a flame ionization detector. Samples were drawn from supply lines leading to exposure chambers and the control chamber at least once every hour. Summaries of chamber concentrations are presented in Table F1.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentration to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured in the 750 ppm exposure chambers with animals present. At a chamber airflow rate of 15 air changes per hour, the theoretical value for both T_{90} and T_{10} is 10 minutes; analysis of chamber concentrations during the first 2 weeks of the studies indicated T_{90} and T_{10} values of 15 minutes; therefore, 15 minutes was used for the T_{90} throughout the studies.

Inhalation chambers were sampled to determine the uniformity of ethylbenzene concentrations; samples from 12 shelf positions within the exposure chambers were analyzed by gas chromatography. Chamber concentration uniformity was maintained throughout the studies.

The persistence of ethylbenzene following exposure was monitored by gas chromatography in the 750 ppm chambers with and without animals present. No ethylbenzene was detectable in the chambers 2 hours after exposure (detection limit 0.44 ppm).

The stability of ethylbenzene was monitored in the generator reservoirs of the 75 and 750 ppm chambers. No significant contaminants or degradation products were found in any of the generator reservoir samples.

Samples from occupied and unoccupied 75 and 750 ppm chambers were analyzed for degradation products before studies began, during the first week of the studies, and every 90 days thereafter. One small impurity was detected in samples taken from the 750 ppm chambers.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female F344/N rats and $B6C3F_1$ mice were exposed by inhalation to 0, 75, 250, and 750 ppm ethylbenzene for 6 hours plus T_{90} (15 minutes) per day, 5 days per week, for 103 (mice) or 104 (rats) weeks. The high exposure concentration selected for these studies was 750 ppm ethylbenzene, roughly 19% of the 4-hour LC_{50} for rats reported by Smyth *et al.* (1962). Following the last day of exposure, rats and mice were observed for 9 to 12 days prior to necropsy.

Source and Specification of Animals

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix H).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages were rotated once weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

Animals were observed twice daily. Clinical findings were recorded approximately monthly. Body weights were recorded initially, weekly for the first 13 weeks, at week 16, monthly through the end of exposure, and prior to terminal necropsy. A complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal

gland, kidney, and ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. A quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney, liver, lung, and nose of male and female rats; bone marrow, parathyroid gland, prostate gland, and testis of male rats; pituitary gland of female rats; heart, kidney, liver, lung, nose, and thyroid gland of male and female mice; and pituitary gland of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on 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 found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B4, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm 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 the fit of the model was not significantly enhanced. The neoplasm incidences of exposed 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 neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

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

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

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of ethylbenzene was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of ethylbenzene are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms

of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. However, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Ethylbenzene

Study Laboratory
IIT Research Institute (Chicago, IL)

Strain and Species
Rats: F344/N
Mice: B6C3F$_1$

Animal Source
Simonsen Laboratories, Inc. (Gilroy, CA)

Time Held Before Studies
Rats: 13 days
Mice: 11 days

Average Age When Studies Began
Rats: 6 weeks
Mice: 6 weeks

Date of First Exposure
Rats: 7 March 1990
Mice: 5 March 1990

Duration of Exposure
Rats: 5 days per week for 104 weeks
Mice: 5 days per week for 103 weeks

Date of Last Exposure
Rats: 28 February 1992
Mice: 21 February 1992

Necropsy Dates
Rats: 9-11 March 1992
Mice: 2-5 March 1992

Average Age at Necropsy
Rats: 111 weeks
Mice: 110 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
NIH-07 open formula pelleted diet (Zeigler Brothers Inc., Gardners, PA), available *ad libitum*

Water Distribution
Untreated coarse-filtered City of Chicago drinking water provided via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Ethylbenzene (continued)

Cages
Rats: Models R-16 and R-20 (males) and models R-20 and R-24 (females) stainless steel inhalation cages (Lab Products Inc., Maywood, NJ), rotated weekly
Mice: Model M-40 stainless steel inhalation cages (Lab Products Inc., Maywood, NJ), rotated weekly

Cage Board
Techsorb® (Shepherd Specialty Papers Inc., Kalamazoo, MI)

Chamber Air Supply Filters
Coarse prefilter, activated carbon absorber, and HEPA filter (R & R Equipment Sales, Rosemont, IL)

Inhalation Chambers
Model H-2000® 2 m^3 stainless steel (Lab Products Inc., Maywood, NJ)

Racks
Stainless steel (Lab Products Inc., Maywood, NJ)

Chamber Environment
Temperature: 21° to 28° C (rats)
21° to 27° C (mice)
Relative humidity: 37% to 76% (rats)
32% to 72% (mice)
Fluorescent light: 12 hours/day
Chamber air flow: 500 ± 66 L/minute

Exposure Concentrations
0, 75, 250, or 750 ppm

Type and Frequency of Observation
Observed twice daily; clinical findings recorded approximately monthly; body weights recorded initially, weekly for the first 13 weeks, at week 16, monthly through the end of exposure, and at study termination.

Method of Sacrifice
CO_2 asphyxiation

Necropsy
Necropsy performed on all animals.

Histopathology
Complete histopathologic examinations were performed on all chamber control and exposed rats and mice surviving to the end of the study as well as on animals that died early. In addition to gross lesions and tissue masses, the tissues examined included: adrenal gland, blood vessel (aorta), bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), kidney, larynx, liver, lung, lymph nodes (bronchial, mandibular, mesenteric, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 2). Survival of male rats in the 750 ppm group was significantly less than that of the chamber controls. The survival of male rats followed a negative trend, decreasing with increasing dose.

Body Weights and Clinical Findings

Mean body weights of 250 and 750 ppm males were generally less than those of the chamber controls from week 20 until the end of the study (Figure 3; Tables 3 and 4). The mean body weights of exposed groups of females were generally less than those of the chamber controls during the second year of the study. No clinical findings were attributed to ethylbenzene exposure.

TABLE 2
Survival of Rats in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	28	20	26	26
Natural deaths	7	16	11	22
Animals surviving to study termination	15	14	13	2
Percent probability of survival at the end of the study[a]	30	28	26	4
Mean survival (days)[b]	651	639	651	604
Survival analysis[c]	P < 0.001	P = 0.888	P = 0.953	P < 0.001
Female				
Animals initially in study	50	50	50	50
Missing[d]	0	0	0	1
Moribund	7	14	8	6
Natural deaths	12	5	8	8
Animals surviving to study termination	31[e]	31	34	35
Percent probability of survival at the end of the study	62	62	68	72
Mean survival (days)	661	690	696	706
Survival analysis	P = 0.248N	P = 1.000N	P = 0.620N	P = 0.326N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[d] Censored from survival analyses
[e] Includes one animal that died during the last week of the study

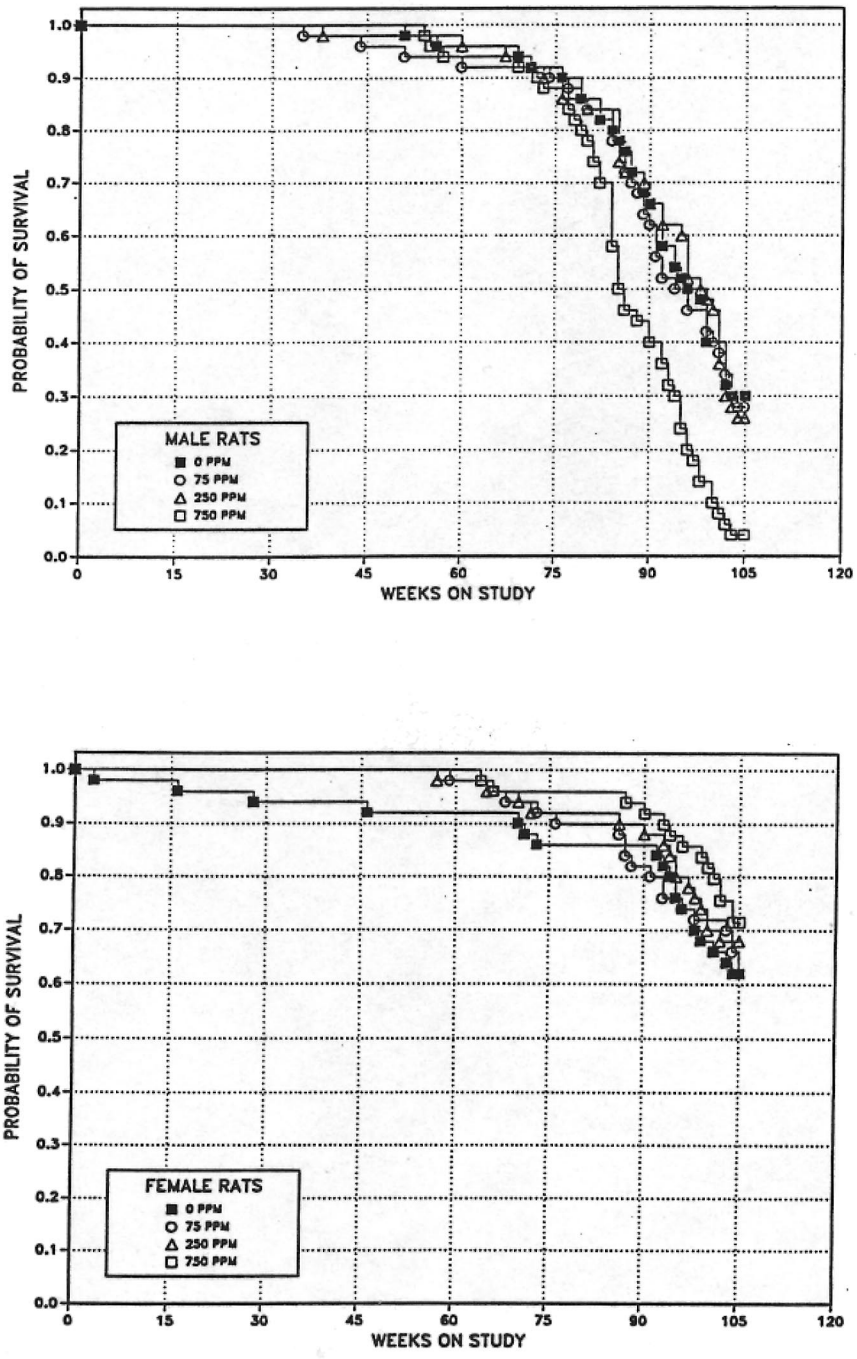


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Ethylbenzene by Inhalation for 2 Years

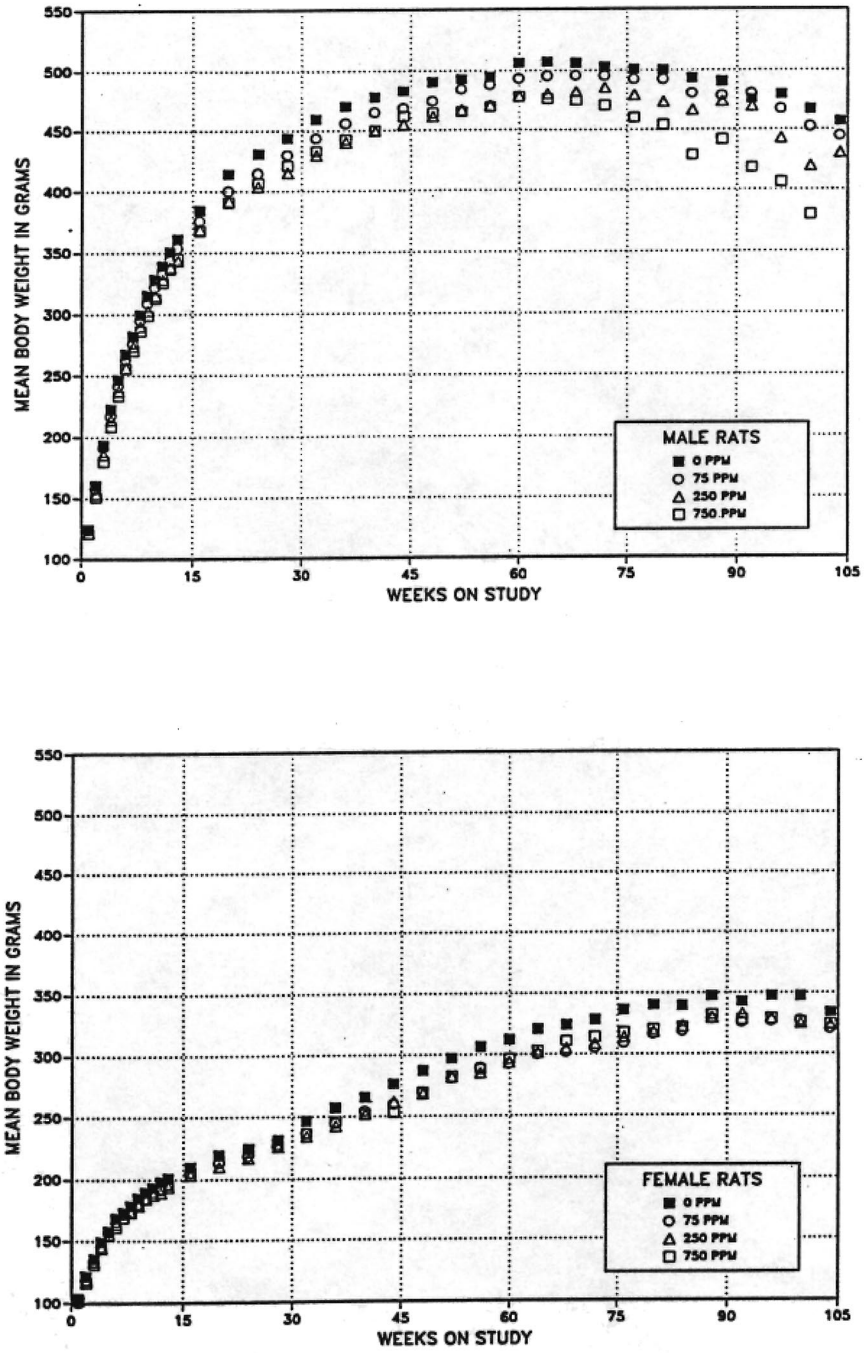


FIGURE 3
Growth Curves for Male and Female Rats Exposed to Ethylbenzene by Inhalation for 2 Years

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Ethylbenzene

Weeks on Study	Chamber Control		75 ppm			250 ppm			750 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	124	50	124	100	50	122	98	50	121	98	50
2	161	50	158	99	50	154	96	50	151	94	50
3	193	50	192	99	50	186	96	50	180	93	50
4	223	50	218	98	50	214	96	50	209	94	50
5	247	50	242	98	50	238	96	50	233	95	50
6	267	50	263	98	50	257	96	50	256	96	50
7	282	50	276	98	50	274	97	50	270	96	50
8	300	50	295	99	50	290	97	50	286	96	50
9	315	50	309	98	50	303	96	50	299	95	50
10	328	50	322	98	50	315	96	50	313	95	50
11	339	50	333	98	50	328	97	50	326	96	50
12	351	50	344	98	50	338	97	50	336	96	50
13	361	50	354	98	50	344	95	50	345	96	50
16	384	50	376	98	50	369	96	50	368	96	50
20	414	50	400	97	50	392	95	50	391	94	50
24	431	50	415	96	50	404	94	50	407	95	50
28	444	50	430	97	50	415	94	50	421	95	50
32	460	50	444	97	50	430	94	50	433	94	50
36	470	50	456	97	49	441	94	50	443	94	50
40	478	50	465	97	49	450	94	49	450	94	50
44	483	50	469	97	49	455	94	49	462	96	50
48	490	50	474	97	48	461	94	49	464	95	50
52	493	49	484	98	47	467	95	49	465	94	50
56	495	49	488	99	47	471	95	49	469	95	48
60	506	48	493	98	47	479	95	49	478	94	47
64	507	48	495	98	46	480	95	48	476	94	47
68	506	48	496	98	46	482	95	47	475	94	47
72	503	46	496	99	46	485	97	46	471	94	46
76	501	46	493	98	45	479	96	44	460	92	44
80	500	43	492	99	43	473	95	43	454	91	39
84	493	41	480	97	41	466	95	42	429	87	35
88	490	36	478	98	35	474	97	36	442	90	23
92	475	33	480	101	27	469	99	33	418	88	20
96	480	26	467	98	25	443	92	30	406	85	12
100	467	20	452	97	20	420	90	24	380	81	7
104	457	15	445	97	14	431	94	14	417	91	2
Mean for weeks											
1-13	269		264	98		259	96		256	95	
14-52	455		441	97		428	94		430	95	
53-104	491		481	98		466	95		444	90	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Ethylbenzene

Weeks on Study	Chamber Control		75 ppm			250 ppm			750 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	104	50	100	97	50	104	100	50	102	98	50
2	122	50	119	98	50	119	98	50	116	96	50
3	135	50	134	99	50	133	99	50	131	97	50
4	149	49	146	98	50	145	97	50	144	96	50
5	158	49	157	99	50	156	99	50	154	98	50
6	168	49	166	98	50	164	97	50	161	96	50
7	173	49	172	99	50	169	98	50	170	98	50
8	179	49	176	98	50	173	97	50	174	98	50
9	185	49	180	98	50	179	97	50	180	98	50
10	190	49	185	98	50	184	97	50	185	98	50
11	194	49	190	98	50	188	97	50	188	97	50
12	198	49	193	98	50	189	96	50	192	97	50
13	201	49	196	98	50	194	97	50	196	97	50
16	210	49	206	98	50	204	97	50	206	98	50
20	220	48	213	97	50	210	96	50	215	98	50
24	225	48	219	97	50	217	97	50	222	99	50
28	231	48	227	98	50	226	98	50	229	99	50
32	247	47	237	96	50	234	95	50	237	96	50
36	257	47	245	95	50	243	94	50	246	96	50
40	266	47	255	96	50	252	95	50	252	95	50
44	276	47	260	94	50	262	95	50	253	92	50
48	287	46	270	94	50	269	94	50	269	94	50
52	297	46	281	95	50	282	95	50	283	95	50
56	306	46	290	95	50	285	93	50	288	94	50
60	312	46	293	94	49	294	94	49	296	95	50
64	321	46	300	94	49	301	94	49	303	95	50
68	324	46	302	93	48	305	94	48	311	96	48
72	328	44	305	93	47	308	94	47	314	96	48
76	336	43	309	92	46	314	94	46	317	94	47
80	340	43	317	93	45	318	94	46	320	94	47
84	340	43	319	94	45	323	95	46	322	95	47
88	347	43	329	95	41	330	95	45	332	96	46
92	343	42	326	95	40	333	97	44	328	96	45
96	347	37	327	94	37	329	95	40	329	95	42
100	347	34	327	94	36	325	94	36	326	94	41
104	334	32	320	96	34	324	97	34	325	97	35
Mean for weeks											
1-13	166		162	98		161	97		161	97	
14-52	252		241	96		240	95		241	96	
53-104	333		313	94		315	95		316	95	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia as well as neoplasms and/or nonneoplastic lesions of the kidney, testis, and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Kidney: In male rats exposed to 750 ppm, the incidences of renal tubule proliferative lesions were significantly increased relative to those in the chamber control group (Tables 5 and A3). The incidences of renal tubule adenoma and adenoma or carcinoma (combined) in this group were significantly greater than the chamber control group incidences. Renal tubule carcinomas were found in four exposed male rats, one in the 250 ppm group and three in the 750 ppm group. The incidences of renal tubule adenoma in 75 and 750 ppm males, renal tubule carcinoma in 250 and 750 ppm males, and renal tubule adenoma or carcinoma (combined) in all exposed groups of males exceeded the historical control ranges (Tables 5 and A4a). In addition, the incidence of renal tubule hyperplasia in 750 ppm males was significantly greater than that in the chamber control group (Tables 5 and A5).

Renal tubule hyperplasia, adenoma, and carcinoma constitute a morphologic and biologic continuum. Hyperplasia was a focal lesion consisting of tubules which were enlarged up to two to three times the diameter of a normal tubule and which were lined by increased numbers of epithelial cells that partially or totally filled the tubule lumen (Plate 1). Hyperplasia was considered a preneoplastic lesion and was distinguished from regenerative epithelial changes commonly seen as a component of chronic nephropathy. Renal tubule adenomas were discrete proliferative lesions, which were larger than focal hyperplasia and which tended to form more complex, usually multilobulated structures (Plate 2). Most adenomas ranged in size from 0.4 to 1 mm in size. Carcinomas were macroscopic tumors, 0.5 to 1.5 cm in size, which projected beyond the capsular surface (Plate 3). Microscopically, carcinomas were characterized by more pleomorphic cells, more prominent vascular supply, and large central areas of necrosis (Plate 4).

Initially, a single section of each kidney was examined microscopically. Because of the increased incidences of proliferative lesions in exposed males and a suggestion of a similar effect in females, additional step sections of kidney were prepared from remaining formalin-fixed tissues. Four additional sections per kidney from each male and female rat were prepared and examined. Numerous additional incidences of focal hyperplasia and adenoma were identified in the kidneys of both males and females. The incidences of these proliferative lesions observed in the extended evaluation and the combined incidences of standard and step sections are presented in Table 5. In males, there were significant increases in the incidences of renal tubule adenoma and hyperplasia in the step sections of the 750 ppm group compared to those of the chamber controls. Incidences of multiple adenomas were found in both 250 and 750 ppm males. No additional renal tubule carcinomas were identified. In the extended evaluation of females, additional incidences of renal tubule adenoma were found only in the 250 and 750 ppm groups, and the adenoma incidence in the 750 ppm group was significantly increased over chamber controls in which no adenomas were identified in either the standard or step sections. The incidence of renal tubule hyperplasia in the extended evaluation was also significantly increased in 750 ppm females.

The severities of nephropathy in 750 ppm male and all exposed female rats were significantly increased relative to chamber controls (Table 5). Nephropathy was characterized by a spectrum of changes, including dilation of renal tubules with hyaline or cellular casts, interstitial fibrosis and mononuclear inflammatory cell infiltration, foci of tubular regeneration, and transitional epithelial hyperplasia of the renal papilla. The enhanced nephropathy was more severe in males than in females, generally moderate to marked in severity, and involved most of the renal parenchyma. Several nonrenal changes which were considered secondary to the exacerbated nephropathy in 750 ppm males were significantly increased in severity relative to controls, including parathyroid gland hyperplasia, mineralization of blood vessel walls and the stomach, and fibrous osteodystrophy of bone.

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control		75 ppm		250 ppm		750 ppm	
Male								
Number Examined Microscopically	50		50		50		50	
Single Sections (Standard Evaluation)								
Nephropathy[a]	47	(2.3)[b]	43	(2.4)	47	(2.3)	48	(3.5)**
Renal Tubule Hyperplasia	2	(3.0)	2	(2.0)	4	(1.3)	12**	(1.8)
Renal Tubule Adenoma[c]	0		3		2		4*	
Renal Tubule Carcinoma[d]	0		0		1		3	
Renal Tubule Adenoma or Carcinoma[c]	0		3		3		7**	
Step Sections (Extended Evaluation)								
Renal Tubule Hyperplasia	10		7		9		17*	
Renal Tubule Adenoma, Multiple	0		0		2		4	
Renal Tubule Adenoma (includes multiple)	3		2		7		17**	
Renal Tubule Carcinoma	0		0		1		3	
Renal Tubule Adenoma or Carcinoma	3		2		8		18**	
Single Sections and Step Sections (Combined)								
Renal Tubule Hyperplasia	11	(2.0)	9	(2.3)	11	(2.1)	23**	(2.5)
Renal Tubule Hyperplasia, Oncocytic	2	(3.0)	3	(2.3)	0		1	(2.0)
Renal Tubule Adenoma, Multiple	0		0		2		4	
Renal Tubule Adenoma (includes multiple)	3		5		7		20**	
Renal Tubule Carcinoma	0		0		1		3	
Renal Tubule Adenoma or Carcinoma	3		5		8		21**	
Oncocytoma	0		1		1		2	
Female								
Number Examined Microscopically	50		50		50		49	
Single Sections (Standard Evaluation)								
Nephropathy	38	(1.3)	42	(1.6)*	43	(1.7)**	46	(2.3)**
Renal Tubule Hyperplasia	0		1	(1.0)	3	(2.3)	3	(1.3)
Renal Tubule Adenoma	0		0		0		1	
Step Sections (Extended Evaluation)								
Renal Tubule Hyperplasia	1		1		1		8*	
Renal Tubule Adenoma	0		0		1		7*	
Single Sections and Step Sections (Combined)								
Renal Tubule Hyperplasia	1	(1.0)	2	(1.0)	4	(2.2)	10**	(1.8)
Renal Tubule Adenoma	0		0		1		8**	

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test (incidence) or by the Mann-Whitney U test (severity)
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 6/652 (0.9% ± 1.3%); range, 0%-4%
[d] Historical incidence: 0/652

Testis: The incidence of interstitial cell adenoma in 750 ppm males was significantly greater than that in the chamber control group and slightly exceeded the historical control range; the incidence of bilateral testicular adenoma was also significantly increased in 750 ppm males (Tables 6, A3, and A4b). This common neoplasm in male F344/N rats is composed of nodular aggregates of large polyhedral cells with foamy or eosinophilic cytoplasm that extend between and cause compression of the surrounding seminiferous tubules. This neoplasm will develop in nearly all male rats if they are allowed to complete their natural life span; ethylbenzene appeared to enhance its development. The incidence of interstitial cell hyperplasia in 750 ppm males was significantly decreased.

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Rats in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Number Examined Microscopically	50	50	50	50
Interstitial Cell Hyperplasia[a]	14 (1.5)[b]	19 (1.2)	12 (1.3)	8* (1.1)
Bilateral Adenoma				
Overall rate[c]	27/50 (54%)	23/50 (46%)	32/50 (64%)	40/50 (80%)
Adjusted rate[d]	96.0%	91.0%	96.5%	100.0%
Terminal rate[e]	14/15 (93%)	12/14 (86%)	12/13 (92%)	2/2 (100%)
First incidence (days)	608	538	590	500
Logistic regression test[f]	P < 0.001	P = 0.313N	P = 0.177	P < 0.001
Adenoma[g]				
Overall rate	36/50 (72%)	33/50 (66%)	40/50 (80%)	44/50 (88%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	15/15 (100%)	14/14 (100%)	13/13 (100%)	2/2 (100%)
First incidence (days)	497	538	420	483
Logistic regression test	P < 0.001	P = 0.404N	P = 0.194	P = 0.001

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Number of animals with neoplasm per number of animals with testis examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the chamber control column are the P values associated with the trend test. In the exposed group columns are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in an exposure group is indicated by **N**.
[g] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 450/655 (68.7% ± 8.7%); range, 54%-83%

Other organs: The incidences of several nonneoplastic lesions were significantly greater in the 750 ppm males than in chamber controls (Table A5). Incidences of edema (chamber control, 1/50; 75 ppm, 0/50; 250 ppm, 0/50; 750 ppm, 6/50), congestion (1/50, 2/50, 0/50, 6/50), and hemorrhage (0/50, 2/50, 1/50, 8/50) in the lungs as well as hemorrhage in mesenteric (3/49, 5/50, 4/50, 8/50) and renal (0/9, 0/8, 1/9, 8/14) lymph nodes were slightly increased. These circulatory lesions were considered to be agonal changes in moribund animals and not directly related to chemical toxicity. The incidence of cystic degeneration of the liver was also increased in 750 ppm males (15/50, 12/50, 19/50, 30/49); the biologic significance of this increase in the absence of other hepatotoxic changes is unclear.

Compared to the chamber control group, the incidences of prostate gland inflammation in all exposed groups of males were significantly increased (11/50, 29/50, 22/50, 25/50; Table A5). This inflammatory change consisted of infiltration by predominantly mononuclear inflammatory cells into glandular acini and interstitium, increased interstitial fibrosis, and loss of secretory material in affected areas. Relative to chamber controls, males exposed to 75 or 750 ppm exhibited increased incidences of hyperplasia of the bone marrow characterized by hypercellularity due to increased numbers of erythroid and myeloid precursor cells (7/49, 16/49, 9/50, 19/50). The relationship of these changes to ethylbenzene exposure is uncertain due to the lack of clear concentration-dependent responses.

Mononuclear cell leukemia: The incidence of mononuclear cell leukemia was decreased in 750 ppm males (27/50, 26/50, 32/50, 9/50; Table A3). While this decrease was statistically significant by logistic regression, it was not significant by life table analysis, the more appropriate test for this generally fatal neoplasm. This decrease was due in large part to the reduced survival in the 750 ppm group as a result of nephropathy and, therefore, was not considered to be related to ethylbenzene exposure.

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed groups of male and female mice was similar to that of the chamber controls.

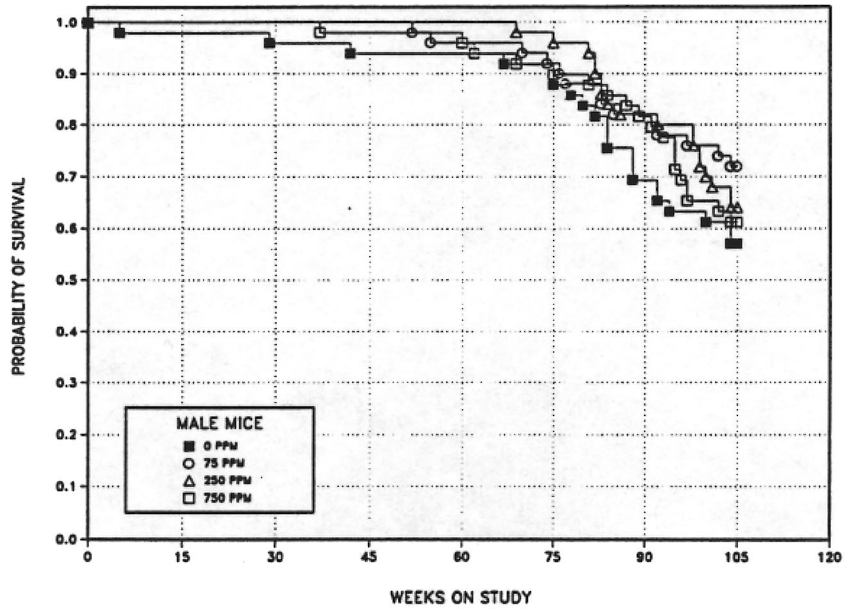
Body Weights and Clinical Findings

Mean body weights of female mice exposed to 75 ppm were greater than those of the chamber controls from week 72 until the end of the study; mean body weights of 750 ppm females were generally less than those of the chamber controls from week 24 through week 68 but were similar to those of the chamber controls from week 72 until the end of the study (Tables 8 and 9; Figure 5). No clinical findings were attributed to ethylbenzene exposure.

TABLE 7
Survival of Mice in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	0	0	1
Moribund	6	2	5	6
Natural deaths	15	12	13	13
Animals surviving to study termination	28	36	32[d]	30
Percent probability of survival at the end of the study[b]	57	72	64	61
Mean survival (days)[c]	636	684	692	665
Survival analysis[e]	P = 0.975	P = 0.177N	P = 0.459N	P = 0.673N
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	1	0	1	0
Moribund	5	6	1	4
Natural deaths	9	6	8	9
Terminal sacrifice	35[d]	38	40	37
Percent probability of survival at the end of the study	71	76	82	74
Mean survival (days)	689	700	701	692
Survival analysis	P = 0.995N	P = 0.762N	P = 0.304N	P = 0.886N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] Includes one animal that died during the last week of the study
[e] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.



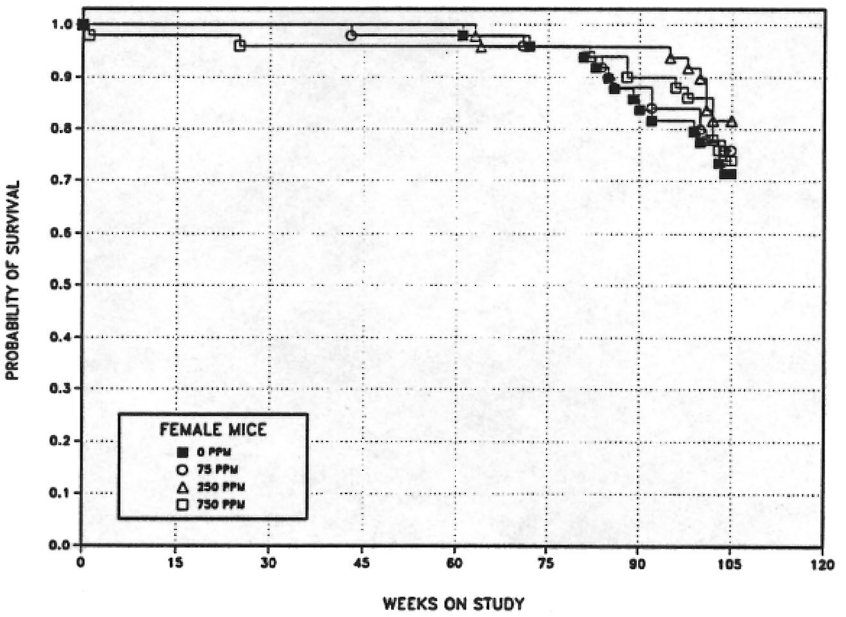


FIGURE 4
Kaplan-Meier survival Curves for Male and Female Mice Exposed to Ethylbenzene by Inhalation for 2 Years

TABLE 8
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Ethylbenzene

Weeks on Study	Chamber Control		75 ppm			250 ppm			750 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.0	50	22.3	97	50	22.9	100	50	22.4	97	50
2	24.9	50	24.2	97	50	25.0	100	50	25.0	100	50
3	26.6	50	26.2	99	50	26.9	101	50	27.3	103	50
4	27.8	50	27.6	99	50	28.1	101	50	28.2	101	50
5	29.0	48	28.8	99	50	29.4	101	50	29.3	101	50
6	30.2	48	30.4	101	50	30.2	100	50	30.1	100	50
7	30.9	48	30.3	98	50	30.7	99	50	31.5	102	50
8	31.6	48	31.5	100	50	31.8	101	50	31.7	100	50
9	32.0	48	32.2	101	50	32.2	101	50	32.3	101	50
10	32.3	48	32.2	100	50	32.4	100	50	33.5	104	50
11	32.8	48	33.5	102	50	33.4	102	50	33.4	102	50
12	33.6	48	33.8	101	50	34.0	101	50	34.1	102	50
13	34.1	48	34.9	102	50	34.8	102	50	34.6	102	50
16	35.7	48	36.4	102	50	36.9	103	50	36.6	103	50
20	38.0	48	38.4	101	50	39.3	103	50	39.0	103	50
24	38.7	48	40.1	104	50	40.2	104	50	39.7	103	50
28	40.4	48	41.4	103	50	41.6	103	50	40.2	100	49
32	41.6	47	44.0	106	50	43.5	105	50	42.5	102	49
36	42.8	47	44.5	104	50	45.0	105	50	44.2	103	49
40	43.9	47	45.3	103	50	45.2	103	50	45.1	103	48
44	45.9	46	46.4	101	50	46.1	100	50	45.6	99	48
48	45.6	46	47.4	104	50	46.9	103	50	47.0	103	48
52	46.7	46	48.5	104	50	47.6	102	50	47.2	101	48
56	47.1	46	47.8	102	48	47.4	101	50	46.7	99	48
60	47.2	46	47.8	101	48	48.6	103	50	46.8	99	48
64	48.1	46	48.6	101	48	48.5	101	50	47.5	99	46
68	47.7	45	48.5	102	48	48.4	102	50	47.9	100	46
72	47.2	45	48.1	102	47	48.5	103	49	48.2	102	45
76	47.0	43	47.7	102	46	48.1	102	48	47.4	101	44
80	46.2	41	48.3	105	44	48.3	105	48	47.2	102	44
84	45.7	40	48.3	106	42	48.6	106	43	48.0	105	42
88	47.9	35	47.9	100	41	48.7	102	41	47.6	99	41
92	47.1	33	46.9	100	41	47.5	101	41	47.7	101	39
96	46.8	31	47.2	101	39	46.8	100	40	46.6	100	35
100	46.7	31	46.6	100	38	45.7	98	36	46.0	99	32
104	45.0	29	44.8	100	37	45.4	101	33	44.0	98	31
Mean for weeks											
1-13	29.9		29.8	100		30.1	101		30.3	101	
14-52	41.9		43.2	103		43.2	103		42.7	102	
53-104	46.9		47.6	101		47.7	102		47.0	100	

TABLE 9
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Ethylbenzene

Weeks on Study	Chamber Control		75 ppm			250 ppm			750 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.5	50	18.6	101	50	18.6	101	50	18.0	97	50
2	20.1	50	19.9	99	50	20.0	100	50	19.5	97	49
3	21.4	50	20.7	97	50	21.1	99	50	21.4	100	49
4	22.4	50	21.6	96	50	22.3	100	50	22.5	100	49
5	23.3	50	22.8	98	50	23.2	100	50	23.5	101	49
6	24.3	50	23.4	96	50	24.2	100	50	23.8	98	49
7	24.4	50	24.0	98	50	24.4	100	50	24.5	100	49
8	25.1	50	24.6	98	50	24.9	99	50	25.1	100	49
9	26.0	50	25.7	99	50	25.6	99	50	26.1	100	49
10	26.0	50	25.4	98	50	25.9	100	50	26.1	100	49
11	26.7	50	26.2	98	50	26.0	97	50	27.0	101	49
12	26.6	50	26.5	100	50	26.7	100	50	26.6	100	49
13	27.3	50	27.2	100	50	26.7	98	49	27.0	99	49
16	28.4	50	28.0	99	50	27.3	96	49	28.8	101	49
20	31.0	50	29.9	97	50	28.8	93	49	30.5	98	49
24	32.0	50	31.2	98	50	29.9	93	49	29.8	93	49
28	33.1	50	32.9	99	50	30.9	93	49	30.5	92	48
32	34.1	49	33.8	99	50	32.5	95	49	31.7	93	48
36	35.7	49	35.5	99	50	35.3	99	49	33.1	93	48
40	36.3	49	36.7	101	50	35.8	99	49	33.4	92	48
44	39.1	49	38.4	98	49	36.8	94	49	35.2	90	48
48	39.8	49	40.0	101	49	40.0	101	49	37.2	94	48
52	40.9	49	41.8	102	49	41.2	101	49	39.4	96	48
56	42.6	49	43.6	102	49	43.0	101	49	39.4	93	48
60	43.1	49	44.4	103	49	43.7	101	49	40.7	94	48
64	44.6	48	45.2	101	49	44.6	100	48	40.5	91	48
68	46.3	48	47.3	102	49	46.5	100	47	43.2	93	48
72	45.6	48	48.6	107	48	47.3	104	47	44.3	97	48
76	46.0	47	48.1	105	48	47.8	104	47	44.4	97	48
80	46.0	47	49.0	107	48	49.5	108	47	44.9	98	48
84	45.8	45	49.8	109	46	49.5	108	47	45.0	98	47
88	45.8	43	50.8	111	44	49.0	107	47	45.2	99	46
92	47.0	40	51.8	110	43	49.9	106	47	45.6	97	45
96	47.0	40	50.3	107	42	49.0	104	46	45.7	97	44
100	47.0	38	49.9	106	42	47.6	101	44	46.4	99	43
104	45.9	36	49.9	109	38	45.2	99	40	45.5	99	37
Mean for weeks											
1-13	24.0		23.6	98		23.8	99		23.9	100	
14-52	35.0		34.8	99		33.9	97		33.0	94	
53-104	45.6		48.4	106		47.1	103		43.9	96	

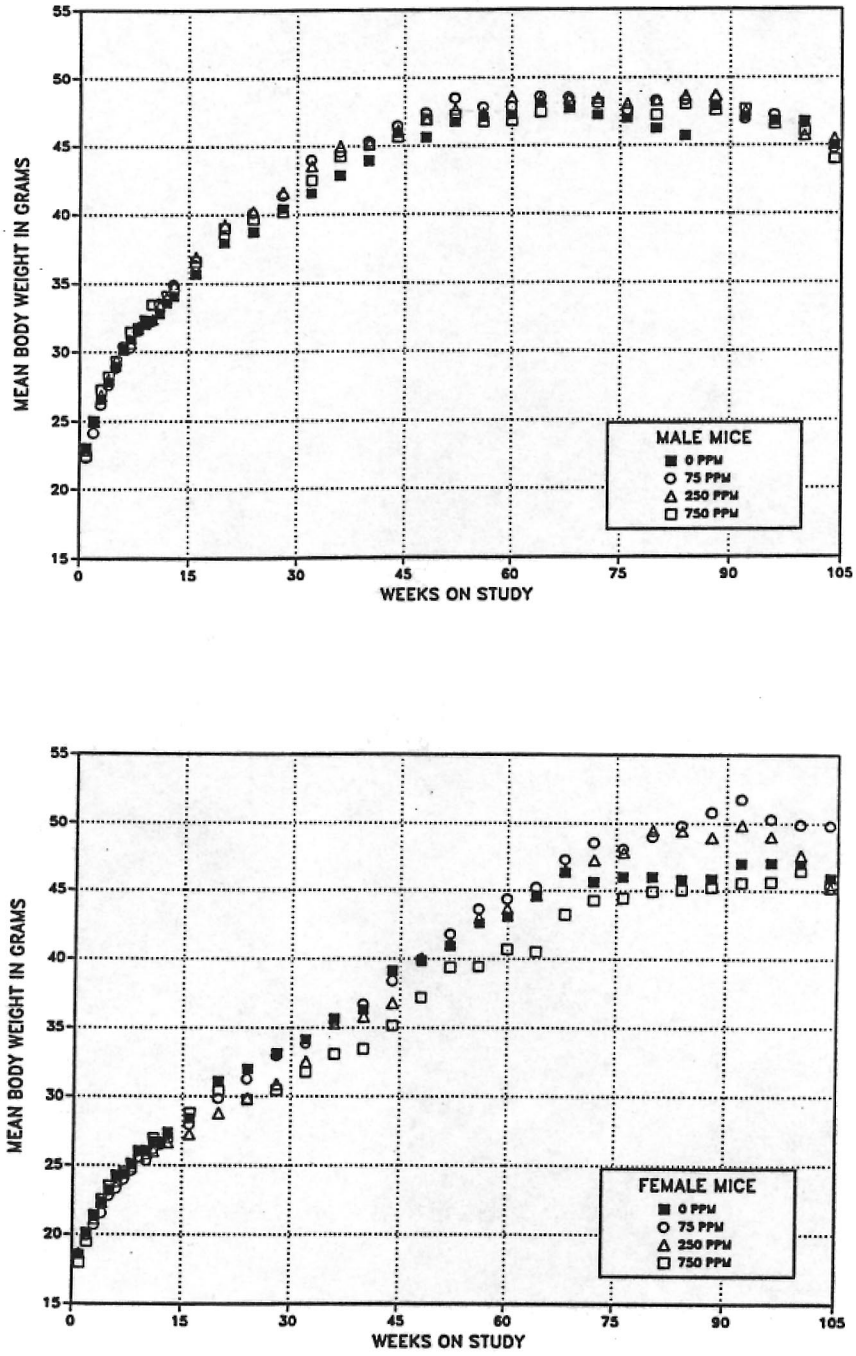


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Ethylbenzene by Inhalation for 2 Years

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the lung, liver, and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analysis of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Lung: Incidences of alveolar/bronchiolar adenoma and alveolar/ bronchiolar adenoma or carcinoma (combined) in males increased with a positive trend (Tables 10 and C3). In 750 ppm males, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater than those in the chamber control group but were within the historical control ranges (Tables 10, C3, and C4). In 750 ppm females, the incidence of alveolar/ bronchiolar adenoma was greater than that in the chamber control group. This difference was not significant, but the incidence exceeded the historical control range (Tables 10, D3, and D4a). Alveolar/bronchiolar neoplasms were nodular proliferations within the lung parenchyma which caused variable compression depending on size (Plate 5). Adenomas were typically well circumscribed nodules composed of monomorphic cuboidal cells arranged in solid or papillary patterns. In carcinomas, the borders were less distinct and the neoplastic cells were cuboidal to columnar in shape and exhibited greater cytologic atypia.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control		75 ppm		250 ppm		750 ppm	
Male								
Number Examined Microscopically	50		50		50		50	
Alveolar Epithelium, Hyperplasia[a]	1	(1.0)[b]	5	(2.6)	2	(1.5)	4	(2.0)
Alveolar Epithelium, Metaplasia	0		1	(1.0)	2	(1.0)	6*	(1.2)
Alveolar/bronchiolar Adenoma[c]	5		9		10		16**	
Alveolar/bronchiolar Carcinoma	2		1		5		3	
Alveolar/bronchiolar Adenoma or Carcinoma[d]	7		10		15		19**	
Female								
Number Examined Microscopically	50		50		49		50	
Alveolar Epithelium, Hyperplasia	0		1	(2.0)	3	(2.0)	1	(3.0)
Alveolar Epithelium, Metaplasia	0		0		0		1	(2.0)
Alveolar/bronchiolar Adenoma[e]	4		4		5		8	
Alveolar/bronchiolar Adenoma or Carcinoma[f]	4		6		5		8	

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
** ($P \leq 0.01$)
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 141/947 (14.9% ± 7.0%); range, 6%-36%
[d] Historical incidence: 205/947 (21.7% ± 8.0%); range, 10%-42%
[e] Historical incidence: 61/939 (6.5% ± 3.2%); range, 0%-14%
[f] Historical incidence: 97/939 (10.3% ± 3.7%); range, 0%-16%

Another proliferative change in the lung was observed only in exposed mice and was diagnosed as alveolar epithelial metaplasia. In males, the incidence of this lesion increased with increasing exposure concentration and was significantly increased in the 750 ppm group (Tables 10 and C5). Alveolar epithelial metaplasia was also observed in one 750 ppm female. Metaplasia was characterized by the presence of cells morphologically similar to bronchiolar epithelial cells lining the alveolar spaces adjacent to terminal bronchioles (Plate 6).

Liver: The incidences of hepatocellular adenoma and adenoma or carcinoma (combined) in females occurred with a positive trend (Table D3). These incidences in 750 ppm females were significantly greater than those in the chamber controls but did not exceed the historical control ranges (Tables 11, D3, and D4b). Although hepatocellular carcinomas also occurred with a positive trend, incidences in exposed groups were not significantly greater than in chamber controls and did not exceed historical control ranges. Multiple adenomas were found in all exposed groups of females, and multiple carcinomas were found in two 750 ppm females, but multiple liver neoplasms were not found in chamber control females. Hepatocellular adenomas consisted of nodules of hepatocytes which compressed adjacent liver parenchyma and lacked the normal lobular and sinusoidal pattern. Hepatocellular carcinomas were large masses composed of anaplastic hepatocytes forming solid sheets or trabecular patterns.

In addition to liver neoplasms, the incidence of eosinophilic foci in the liver was significantly greater in 750 ppm females than in chamber controls (Tables 11 and D5). This lesion, composed of focal collections of cells, which have altered staining characteristics and which blend into surrounding hepatic cords with little or no compression, is considered to be a precursor to hepatocellular neoplasia.

A spectrum of nonneoplastic liver changes related to ethylbenzene exposure in male mice included syncytial alteration of hepatocytes, hepatocellular hypertrophy, and hepatocyte necrosis (Tables 11 and C5). These changes were minimal to mild in severity. Syncytial alteration was seen in all groups of exposed males, with concentration-dependent increases in incidence. This change consisted of the presence of greatly enlarged hepatocytes containing multiple nuclei, generally five or more, either randomly scattered throughout the liver lobule or with a tendency to cluster in centrilobular areas (Plate 7). Hypertrophy of hepatocytes occurred in the centrilobular zones of 750 ppm males and was characterized by cells with increased amounts of cytoplasm and enlarged nuclei. Syncytial alteration and hypertrophy frequently occurred in the same animal. Hepatocellular necrosis was evident as random single cell necrosis, generally of hypertrophied cells.

Other organs: Significantly increased incidences of hyperplasia of the pituitary gland pars distalis were limited to 250 and 750 ppm females (chamber control, 10/48; 75 ppm, 12/49; 250 ppm, 23/47; 750 ppm, 22/49; Table D5). This hyperplasia was seen as focal, poorly delineated, monomorphic increases of cells which had no compressive features or altered arrangement. Positive trends in the incidences of thyroid follicular cell hyperplasia occurred in both males (21/50, 21/50, 29/50, 32/50; Table C5) and females (18/50, 23/50, 25/50, 35/50; Table D5), with significant increases in incidences relative to chamber controls in 750 ppm males and females. Thyroid hyperplasia was typically a focal noncompressive proliferation with simple papillary infoldings of follicular epithelial cells. There were no corresponding increases in the incidences of adenomas of either the pituitary gland or thyroid gland (Tables C1 and D1).

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Male				
Number Examined Microscopically	50	50	50	50
Hepatocyte, Hypertrophy[a]	1 (1.0)[b]	0	0	17** (1.1)
Hepatocyte, Necrosis	1 (1.0)	1 (2.0)	3 (1.3)	10** (1.8)
Hepatocyte, Syncytial Alteration	0	5 (1.0)	8** (1.4)	23** (1.1)
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	5 (1.8)	7 (1.4)	6 (1.5)	22** (2.0)
Hepatocellular Adenoma, Multiple	0	1	3	4
Hepatocellular Adenoma (includes multiple)[c]	6	9	12	16*
Hepatocellular Carcinoma, Multiple	0	0	0	2
Hepatocellular Carcinoma (includes multiple)	7	4	3	12
Hepatocellular Adenoma or Carcinoma[d]	13	12	15	25*

* Significantly different ($P \leq 0.05$) from the chamber control group by the logistic regression test
** ($P \leq 0.01$)
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 114/937 (12.2% ± 9.7%); range, 0%-40%
[d] Historical incidence: 200/937 (21.3% ± 11.9%); range, 3%-54%

GENETIC TOXICOLOGY

Ethylbenzene was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535 with or without Aroclor-induced rat or hamster liver S9 (Table E1; Zeiger *et al.*, 1988). A positive response was observed with ethylbenzene in the L5178Y mouse lymphoma cell assay in the absence of S9 at the highest nonlethal dose tested (80 µg/mL); the assay was not performed with S9 (Table E2; McGregor *et al.*, 1988). A significant amount of cytotoxicity was noted at this dose level (relative total growth was reduced to 34% and 13% of the control level in each of two trials). No increases in sister chromatid exchanges (Table E3) or chromosomal aberrations (Table E4) were induced by ethylbenzene in cultured Chinese hamster ovary cells, with or without S9. *In vivo*, no increases in micronucleated erythrocytes were observed in peripheral blood samples from male and female mice exposed to ethylbenzene for 13 weeks by inhalation (Table E5).

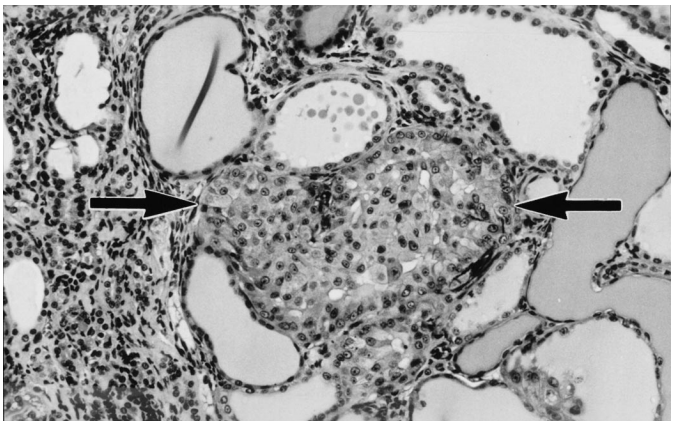


Plate 1
Renal tubule hyperplasia in the kidney of a male F344/N rat exposed to 750 ppm ethylbenzene by inhalation for 2 years. The hyperplastic tubule (between arrows) consists of epithelial cells which fill the lumen. Note the changes of chronic nephropathy in the surrounding parenchyma including dilated tubules and thickened interstitium. H&E; 100×

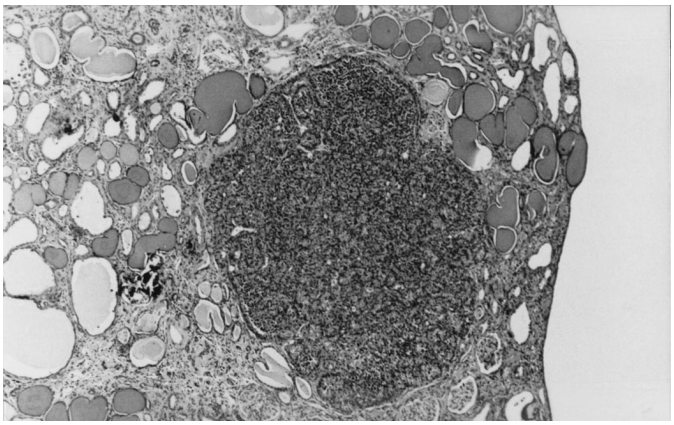


Plate 2
Renal tubule adenoma in the kidney of a male F344/N rat exposed to 750 ppm ethylbenzene by inhalation for 2 years. The adenoma is just under the capsular surface and is well circumscribed and multilobulated. Note the changes of chronic nephropathy in the surrounding parenchyma including dilated tubules filled with protein casts, thickened interstitium, and focal mineralization. H&E; 35×

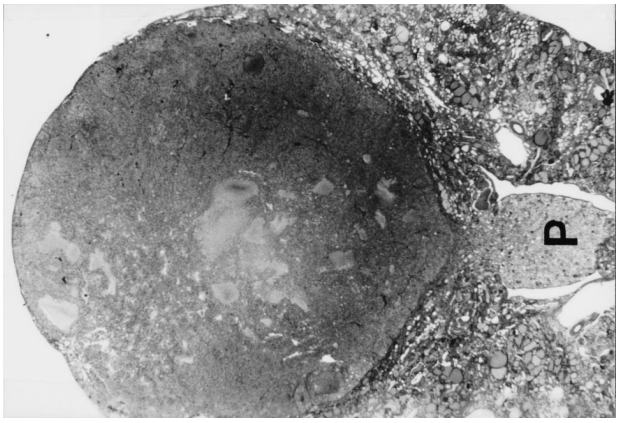


Plate 3
Renal tubule carcinoma in the kidney of a male F344/N rat exposed to 750 ppm ethylbenzene by inhalation for 2 years. The 1 cm diameter mass protrudes coutside the capsular surface and extends deep into the parenchyma near the papilla (P). Note the cystic necrosis of the center. H&E; 6×

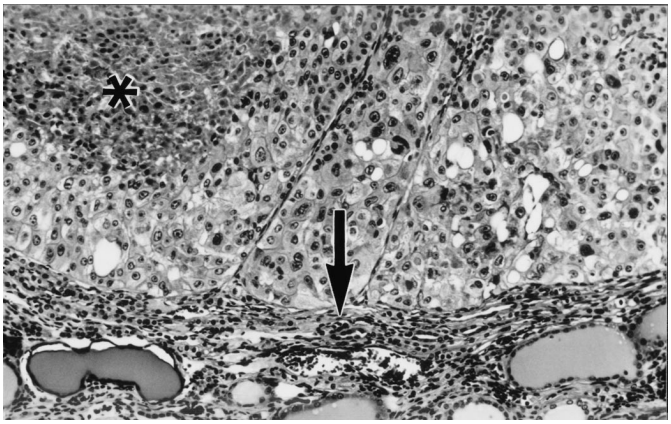


Plate 4
Higher magnification of Plate 3. Irregular lobules of pleomorphic tumor cells are separated by fine septae and compress the surrounding parenchyma (arrow). Note the central necrosis of one lobule (*). H&E; 100×

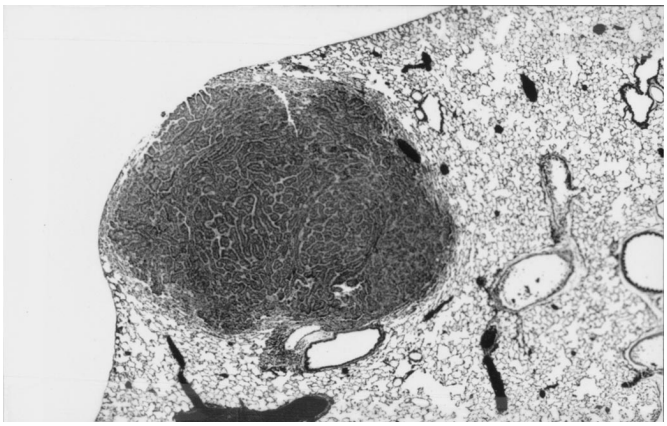


Plate 5
Alveolar/bronchiolar adenoma in the lung of a male B6C3F$_1$ mouse exposed to 750 ppm ethylbenzene by inhalation for 2 years. The adenoma is well demarcated from the adjacent compressed lung parenchyma, and there is bulging of the pleural surface. H&E; 20×

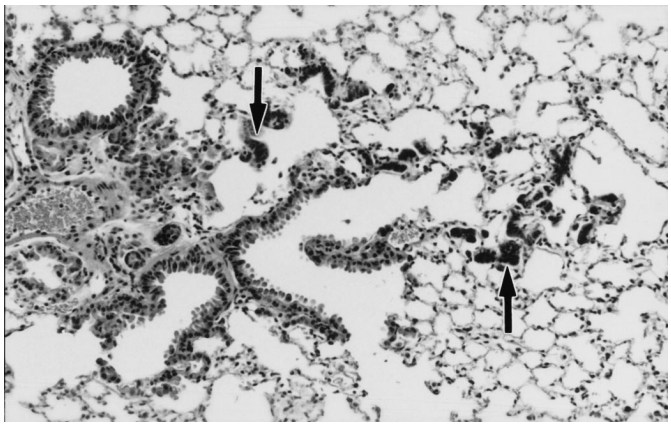


Plate 6
Alveolar epithelial metaplasia in the lung of a male B6C3F$_1$ mouse exposed to 750 ppm ethylbenzene by inhalation for 2 years. Multiple foci of dark-staining epithelial cells (arrows) are in the alveolar spaces adjacent to one branch of a terminal bronchiole bifurcation. H&E; 85×

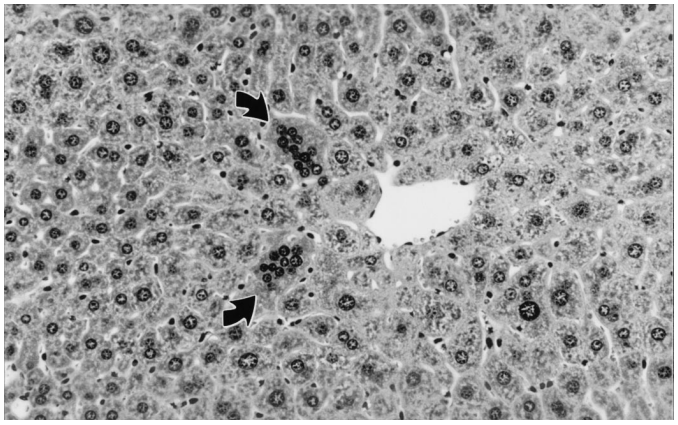


Plate 7
Syncytial alteration of hepatocytes in the liver of a male B6C3F$_1$ mouse exposed to 750 ppm ethylbenzene by inhalation for 2 years. Two large syncytial cells (arrows), each containing approximately 10 nuclei, are adjacent to a central vein. H&E; 140×

DISCUSSION AND CONCLUSIONS

Ethylbenzene is mainly used in the manufacture of styrene. Ethylbenzene is also a major component of mixed xylenes used as solvents in agricultural and home insecticide sprays, rubber and chemical manufacturing, and household degreasers, paints, adhesives, and rust preventives (Fishbein, 1985). Ethylbenzene has been used as an antiknock agent in aviation and motor fuels (NIOSH, 1979).

The National Institute for Occupational Safety and Health and the Occupational Safety and Health Administration nominated ethylbenzene for study because of its widespread human exposure and because of its structural similarity to benzene and toluene.

In previous studies, male and female F344/N rats and $B6C3F_1$ mice were exposed to ethylbenzene by inhalation for 13 weeks at concentrations of 0, 100, 250, 500, 750, or 1,000 ppm (NTP, 1992). In the current studies, male and female F344/N rats and $B6C3F_1$ mice were exposed to ethylbenzene by inhalation for 2 years at concentrations of 0, 75, 250, or 750 ppm.

In the 2-year study, the survival rate and the mean body weights of the 750 ppm male rats were less than those of the chamber control group after week 75 of the study. Female rats generally had higher survival rates than males, and this was probably related to the typical occurrence of nephropathy in male F344/N rats, which was enhanced by ethylbenzene exposure. The mean body weights of exposed groups of female rats were less than those of the chamber controls during the second year of the study. Survival rates of exposed male and female mice were similar to those of the respective chamber controls. Female mice exposed to 75 ppm had greater mean body weights than those of the chamber controls.

In the 13-week studies, increased absolute and relative kidney weights were observed in male rats exposed to 750 or 1,000 ppm ethylbenzene, although no accompanying histopathologic changes were seen (NTP, 1992). In the standard histopathologic evaluation of the kidney in the 2-year study, the incidence of renal tubule adenoma in the 750 ppm male rats was significantly greater than that in the chamber control group. The incidence in 750 ppm males exceeded the NTP historical control range. An extended evaluation of the kidneys in the 2-year study identified many more adenomas. In addition, multiple renal tubule adenomas were found in the 250 and 750 ppm males. The standard evaluation and extended evaluation (combined) showed significantly increased incidences of renal tubule adenoma, renal tubule adenoma or carcinoma (combined), and renal tubule hyperplasia in 750 ppm male rats, as well as positive trends across exposure groups. No renal lesions were observed in females in the NTP 13-week study. In the standard evaluation in the 2-year study, no significant increases in incidences of renal lesions were observed in female rats. In the extended evaluation of the kidneys, the incidences of renal tubule hyperplasia and renal tubule adenoma were significantly increased in the 750 ppm female rats compared to those in the chamber controls.

Kurokawa *et al*. (1983) first reported that a greater incidence of rat kidney lesions was found when multiple kidney sections were examined compared with single sections. This was expected, considering the very small size of many of the tubule cell adenomas typically seen in the kidney. The NTP has compared lesions from single and multiple kidney sections and found increased incidences of renal tubule hyperplasia and renal tubule adenoma in multiple sections from male rats (Eustis *et al.*, 1994), agreeing with the findings of Kurokawa *et al*. (1983). However, few additional neoplasms were identified in female rats or in male or female mice (Eustis *et al.*, 1994). In the present studies, additional incidences of renal tubule hyperplasia and renal tubule adenoma were found in step sections from male and female rats.

Nephropathy is commonly found in aging male and, to a lesser degree, female rats; in the current study, the severities of nephropathy were increased in 750 ppm male rats and in all exposed female rat groups. In the extended evaluation of the kidneys in the 2-year study of ethylbenzene, the incidences of renal tubule hyperplasia in 750 ppm males and females were increased. Ethylbenzene may have

exacerbated the age-related nephropathy development in rats or exerted toxic injury to the renal cells and induced compensatory cell replication of the renal tubule epithelium. Whether they were a direct effect of ethylbenzene or an indirect result of ethylbenzene-induced cytotoxicity, the renal tubule lesions in male and female rats were considered exposure related. Males appeared to be more sensitive to the renal toxic effect of ethylbenzene than females, and that may account for the early deaths in 750 ppm males.

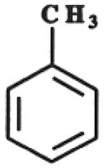
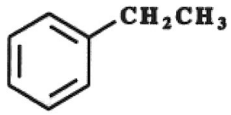
Following exposure to certain hydrocarbons, male rats develop renal tubule hyaline droplets, attributed to accumulation of α2μ-globulin in the kidney. The accumulation of α2μ-globulin is known to lead to nephropathy and renal tubule neoplasm development in male rats. This spectrum of nonneoplastic changes differs from the chronic progressive nephropathy commonly found in aging male rats (USEPA, 1991). No clear evidence of hyaline droplets was seen in the kidneys of male F344/N rats exposed to ethylbenzene for 13-weeks (NTP, 1992) or 2 years, and, thus, this proposed mechanism did not appear to contribute to the proliferative renal tubule lesions in male or female F344/N rats in the studies reported here.

After a 6-hour inhalation exposure to ethylbenzene in male Wistar rats, the major metabolites identified in the urine were 1-phenylethanol (α-methylbenzyl alcohol), mandelic acid, phenylglyoxylic acid, phenylacetic acid, and benzoic acid. Minor metabolites included omega-hydroxyacetophenone, 1-phenyl-1,2-ethanediol, acetophenone, p-hydroxyacetophenone, and phenylglyoxal. Blood metabolites were difficult to identify and measure (Engström, 1984). None of the urinary metabolites, except 1-phenylethanol, are considered ultimate carcinogens likely reactive with cellular macromolecules. Ethylbenzene is neither mutagenic nor clastogenic. Both 1- and 2-phenylethanol were negative for mutagenicity and did not induce sister chromatid exchanges in cultured human lymphocytes (NTP, 1990b; Norppa and Vainio, 1983). It is possible that in the process of metabolizing ethylbenzene to 1- and 2-phenylethanol, an epoxide intermediate is formed. A gender difference in epoxide formation may account for the differential sensitivity for neoplasia between the male and female mouse lungs.

α-Methylbenzyl alcohol (1-phenylethanol), a metabolite of ethylbenzene (Engström, 1984), has been shown to enhance nephropathy and induce renal tubule adenoma or adenocarcinoma in male F344/N rats (NTP, 1990b) but had no effect on nephropathy or renal tubule lesions in female F344/N rats. Since kidney toxicity and carcinogenicity were observed in both male and female rats in the present studies, the data suggested that the renal effect of ethylbenzene is more potent than that of α-methylbenzyl alcohol. Other metabolites, such as an epoxide or diolepoxide after ring oxidation (Engström, 1984), phenylglyoxal bearing a reactive aldehyde group, or those metabolites postulated in benzene metabolism, such as hydroquinone, benzoquinone, or benzene diolepoxide (NTP, 1986; Busby *et al.*, 1990), may contribute to the renal toxicity and carcinogenicity of ethylbenzene. However, no reactive metabolite has been identified. Further studies to identify the active species are needed. It should be noted that neither ethylbenzene nor α-methylbenzyl alcohol is mutagenic or clastogenic.

Structurally, ethylbenzene is related to benzene and toluene (Table 12). Toluene is negative for carcinogenic activity (NTP, 1990a). Benzene is a multipotential carcinogen suppressing bone marrow cellularity and inducing leukopenia and leukemia and neoplasms in the Zymbal's gland, oral cavity, and skin in rats and Zymbal's gland, lymph gland, lung, harderian gland, preputial gland, mammary gland, ovary, forestomach, and liver in mice after gavage dosing (NTP, 1986). Benzene is metabolized to benzene oxide, benzene oxepin, benzene dihydrodiol, phenol, hydroquinone, trihydroxybenzene, catechol, benzoquinone, and *trans*,*trans*-muconaldehyde (Snyder and Hedli, 1996; Sabourin *et al.*, 1989, 1992). The metabolites proposed for the hematotoxicity in rats are hydroquinone, benzoquinone, and *trans*,*trans*-muconaldehyde (Zhu *et al.*, 1995), and for lung tumors in mice, the metabolite is benzene diolepoxide-2 (Busby *et al.*, 1990). Although benzene and ethylbenzene are structurally related, the metabolites, target organs, and mechanism of action of benzene appear quite different from those of ethylbenzene.

TABLE 12
Results of Carcinogenicity and Mutagenicity Tests of Benzene, Toluene, and Ethylbenzene in Male and Female F344/N Rats and Male and Female B6C3F Mice in 2-Year Studies 1 [a]

	Carcinogenicity				*Salmonella*
Chemical and Route	Male Rat	Female Rat	Male Mouse	Female Mouse	Test Result
Benzene (gavage) (NTP, 1986) 	+ Zymbal's gland, oral cavity, skin	+ Zymbal's gland, oral cavity	+ Zymbal's gland, lymph gland, lung, harderian gland, preputial gland, forestomach	+ Zymbal's gland, lymph gland, lung, harderian gland, mammary gland, ovary, forestomach, liver	—
Toluene (inhalation) (NTP, 1990a) 	—	—	—	—	—
Ethylbenzene (inhalation) 	+ kidney, testis	+ kidney	+ lung	+ liver	—

[a]**Carcinogenic response: + = some or clear evidence of carcinogenic activity; — = no evidence of carcinogenic activity**

The increased incidence of testicular adenoma observed in male rats in the 750 ppm group was considered related to ethylbenzene exposure. This is evidenced by the finding that 92% (22/24) of the 750 ppm male rats that died between days 400 and 600 had testicular adenoma, whereas only 33% (3/9) of the chamber controls that died early had testicular adenoma. The incidence of bilateral adenoma was also increased in 750 ppm males. Testicular adenoma develops in nearly all rats in the latter part of their lives, but in inhalation studies, the incidence is low compared with those in feed and gavage studies (Haseman et al., 1997); ethylbenzene appeared to hasten the development of testicular adenoma. How ethylbenzene accomplishes this effect is not clear. There were no testicular effects detected in the 13-week studies (NTP, 1992). α-Methylbenzyl alcohol, a metabolite of ethylbenzene, may not be involved because it inhibits testicular adenoma (NTP, 1990b).

In addition to inducing renal tubule neoplasms in rats, ethylbenzene exposure may have induced bone marrow hyperplasia characterized by hypercellularity of erythroid and myeloid precursor cells. Cragg et al. (1989) also reported that Fischer 344/N rats exposed

to ethylbenzene at 782 ppm for 4 weeks had a small increase in leukocyte counts. On the other hand, ethylbenzene depressed mononuclear cell leukemia in 750 ppm males, but this was considered to be due largely to reduced survival in this group.

In the 2-year mouse studies, the incidences of alveolar epithelial metaplasia and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased in 750 ppm male mice but not in 750 ppm female mice. Estimated differences in inhaled air volume alone (male mice have a greater ventilation volume per body weight than do female mice) could not explain the difference between males and females in their responses to ethylbenzene inhalation.

The incidence of hepatocellular adenoma or carcinoma (combined) was significantly greater in the 750 ppm group of female mice compared to that in the chamber controls. The incidence of liver eosinophilic foci was also significantly greater in the 750 ppm group of female mice. A significant increase in absolute liver weight was observed in male and female mice exposed to ethylbenzene at 750 ppm and higher in the 13-week studies (NTP, 1992). Increased absolute and relative liver weights were also reported in female $B6C3F_1$ mice exposed to ethylbenzene by inhalation (Cragg *et al.*, 1989). The female mouse liver appears to be more sensitive to the effects of ethylbenzene.

It is also not clear why male and female $B6C3F_1$ mice had different neoplasm responses to ethylbenzene exposure. There are little data available on which to judge why ethylbenzene affected the male and female endocrine systems differently, although an exposure-related increase in the incidence of pituitary gland (pars distalis) hyperplasia was seen in female mice. Ethylbenzene induced an exposure-related increase in the incidences of hyperplasia in the thyroid gland of male and female mice, but there was no difference between males and females in incidence observed.

Phenylglyoxylic and mandelic acids were effective in causing brain dopamine depletion *in vitro* (Mutti and Franchini, 1987) and *in vivo* (Mutti *et al.*, 1988). On the other hand, Andersson *et al.* (1981) reported that male Sprague-Dawley rats exposed to ethylbenzene by inhalation at 2,000 ppm, 6 hours per day for 3 days had increases in dopamine and noradrenaline levels in the hypothalamus and the median eminence. Such neurotoxic effects would disturb brain function and cause neurobehavioral and neuroendocrine changes and may be related to the gender difference in response to ethylbenzene exposure.

The gender and species differences and organ specificity in the carcinogenic effects of ethylbenzene are unexpected findings. The mechanisms of action of ethylbenzene carcinogenesis in rats and mice remain to be defined.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *clear evidence of carcinogenic activity** of ethylbenzene in male F344/N rats based on increased incidences of renal tubule neoplasms. The incidences of testicular adenoma were also increased. There was *some evidence of carcinogenic activity* of ethylbenzene in female F344/N rats based on increased incidences of renal tubule adenomas. There was *some evidence of carcinogenic activity* of ethylbenzene in male $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *some evidence of carcinogenic activity* of ethylbenzene in female $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms.

Exposure of male and female rats to ethylbenzene resulted in increased incidences of renal tubule hyperplasia and increased severities of nephropathy. Exposure of male mice to ethylbenzene resulted in increased incidences of alveolar epithelial metaplasia, syncytial alteration of hepatocytes, hepatocellular hypertrophy, hepatocyte necrosis, and thyroid gland follicular cell hyperplasia. In female mice, ethylbenzene exposure resulted in increased incidences of eosinophilic foci of the liver, pituitary gland pars distalis hyperplasia, and thyroid gland follicular cell hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF ETHYLBENZENE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	28	20	26	26
Natural deaths	7	16	11	22
Survivors				
Terminal sacrifice	15	14	13	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(48)	(48)	(48)
Sarcoma	1 (2%)			
Intestine large, rectum	(48)	(49)	(48)	(48)
Intestine large, cecum	(46)	(44)	(46)	(39)
Intestine small, duodenum	(48)	(48)	(50)	(50)
Intestine small, jejunum	(42)	(39)	(44)	(34)
Intestine small, ileum	(45)	(44)	(45)	(37)
Liver	(50)	(50)	(50)	(49)
Hepatocellular adenoma		3 (6%)		
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, spleen	1 (2%)			
Mesentery	(4)	(5)	(3)	(3)
Lipoma			1 (33%)	
Sarcoma	1 (25%)			
Oral mucosa	(2)		(1)	(1)
Pharyngeal, squamous cell papilloma	2 (100%)		1 (100%)	1 (100%)
Pancreas	(50)	(49)	(50)	(50)
Duct, carcinoma		1 (2%)		
Salivary glands	(50)	(49)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(49)	(50)	(50)
Tongue	(1)			
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Osteosarcoma, metastatic, spleen	1 (2%)			
Adrenal medulla	(50)	(50)	(49)	(48)
Osteosarcoma, metastatic, spleen	1 (2%)			
Pheochromocytoma malignant		1 (2%)		2 (4%)
Pheochromocytoma benign	6 (12%)	10 (20%)	6 (12%)	9 (19%)
Bilateral, pheochromocytoma benign	7 (14%)	3 (6%)	3 (6%)	3 (6%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	4 (8%)	4 (8%)	4 (8%)
Carcinoma	2 (4%)	1 (2%)		
Parathyroid gland	(45)	(46)	(46)	(46)
Adenoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Endocrine System (continued)				
Pituitary gland	(49)	(50)	(50)	(45)
Pars distalis, adenoma	23 (47%)	18 (36%)	18 (36%)	18 (40%)
Pars distalis, adenoma, multiple	2 (4%)	1 (2%)	1 (2%)	
Thyroid gland	(50)	(49)	(50)	(50)
Bilateral, C-cell, adenoma	2 (4%)			
C-cell, adenoma	1 (2%)	6 (12%)	3 (6%)	2 (4%)
C-cell, carcinoma	2 (4%)			
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
Peritoneum		(1)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(49)	(50)	(49)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	2 (4%)
Bilateral, adenoma				2 (4%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(49)	(49)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	27 (54%)	23 (46%)	32 (64%)	40 (80%)
Interstitial cell, adenoma	9 (18%)	10 (20%)	8 (16%)	4 (8%)
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node	(9)	(8)	(9)	(14)
Lymph node, bronchial	(44)	(34)	(39)	(28)
Histiocytic sarcoma		1 (3%)		
Lymph node, mandibular	(47)	(48)	(49)	(50)
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node, mediastinal	(48)	(48)	(50)	(47)
Histiocytic sarcoma		1 (2%)		
Spleen	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Osteosarcoma	1 (2%)			
Thymus	(46)	(44)	(46)	(44)
Histiocytic sarcoma		1 (2%)		
Thymoma benign			1 (2%)	
Integumentary System				
Mammary gland	(46)	(47)	(46)	(49)
Adenoma			1 (2%)	
Fibroadenoma	2 (4%)	2 (4%)	2 (4%)	
Fibroadenoma, multiple		1 (2%)		
Fibroma		2 (4%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma			1 (2%)	
Basal cell carcinoma				1 (2%)
Keratoacanthoma	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Squamous cell papilloma	2 (4%)	1 (2%)	1 (2%)	
Pinna, schwannoma benign		1 (2%)		
Pinna, schwannoma malignant			1 (2%)	
Sebaceous gland, adenoma			1 (2%)	
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	3 (6%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, myxoma			1 (2%)	
Subcutaneous tissue, sarcoma		2 (4%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Turbinate, chondroma			1 (2%)	
Skeletal muscle	(1)	(1)		(1)
Histiocytic sarcoma		1 (100%)		
Osteosarcoma, metastatic, spleen	1 (100%)			
Sarcoma				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Glioma malignant			1 (2%)	1 (2%)
Respiratory System				
Larynx	(40)	(44)	(41)	(35)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, thyroid gland	2 (4%)			
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, spleen	1 (2%)			
Mediastinum, osteosarcoma, metastatic, spleen	1 (2%)			
Nose	(49)	(49)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)	
Special Senses System				
Harderian gland			(1)	
Carcinoma			1 (100%)	
Zymbal's gland	(1)		(1)	(1)
Carcinoma	1 (100%)		1 (100%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lipoma	1 (2%)			
Renal tubule, adenoma		3 (6%)	2 (4%)	4 (8%)
Renal tubule, carcinoma			1 (2%)	3 (6%)
Urinary bladder	(49)	(49)	(50)	(49)
Transitional epithelium, papilloma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Leukemia mononuclear	27 (54%)	26 (52%)	32 (64%)	9 (18%)
Mesothelioma malignant		2 (4%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	45	50	50
Total primary neoplasms	134	131	134	111
Total animals with benign neoplasms	48	44	48	48
Total benign neoplasms	97	95	94	93
Total animals with malignant neoplasms	33	32	37	17
Total malignant neoplasms	37	36	40	18
Total animals with metastatic neoplasms	3			
Total metastatic neoplasms	8			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control

Number of Days on Study	3 5 4	3 9 1	4 7 9	4 9 7	5 2 8	5 4 7	5 5 3	5 7 0	5 7 4	5 8 4	5 9 0	6 0 2	6 0 8	6 0 9	6 1 8	6 2 3	6 3 0	6 3 9	6 4 0	6 4 0	6 4 4	6 5 2	6 5 3	6 6 1	6 6 8
Carcass ID Number	0 4 8	0 3 8	0 0 9	0 3 9	0 2 5	0 0 8	0 2 4	0 4 5	0 3 6	0 5 0	0 1 9	0 0 3	0 2 3	0 0 5	0 2 9	0 3 2	0 2 7	0 4 1	0 0 4	0 2 8	0 1 1	0 1 2	0 4 4	0 1 4	0 2 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen											X														
Mesentery				+																					
Sarcoma				X																					
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue								+																	
Squamous cell papilloma								X																	
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen											X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, spleen											X														
Pheochromocytoma benign										X						X								X	
Bilateral, pheochromocytoma benign													X												X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma											X														
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X	X	X					X		X	X	X						X	X		
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																									
C-cell, carcinoma																								X	
Follicular cell, carcinoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	6 8 5	6 8 9	6 8 9	6 8 9	6 9 2	7 1 0	7 1 0	7 1 3	7 1 4	7 1 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 0 1	0 1 7	0 3 3	0 1 3	0 0 2	0 3 4	0 0 6	0 4 6	0 4 7	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 0	0 2 1	0 2 6	0 3 0	0 3 1	0 3 5	0 3 7	0 4 0	0 4 2	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																				X						1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Mesentery			+																+						+	4
Sarcoma																										1
Oral mucosa			+																						+	2
Pharyngeal, squamous cell papilloma			X																						X	2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, spleen																										1
Pheochromocytoma benign										X									X	X						6
Bilateral, pheochromocytoma benign		X	X			X					X					X										7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X			X																X		3
Carcinoma										X																2
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X	X	X	X	X	X	X		X		X			X	X			X		23
Pars distalis, adenoma, multiple		X												X												2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																			X	X						2
C-cell, adenoma													X													1
C-cell, carcinoma									X																	2
Follicular cell, carcinoma																									X	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	3 5 4	3 9 1	4 7 9	4 9 7	5 2 8	5 4 7	5 5 3	5 7 0	5 7 4	5 8 4	5 9 0	6 0 2	6 0 8	6 0 9	6 1 8	6 2 3	6 3 0	6 3 9	6 4 0	6 4 0	6 4 4	6 5 2	6 5 3	6 6 1	6 6 8
Carcass ID Number	0 4 8	0 3 8	0 0 9	0 3 9	0 2 5	0 0 8	0 2 4	0 4 5	0 3 6	0 5 0	0 1 9	0 0 3	0 2 3	0 0 5	0 2 9	0 3 2	0 2 7	0 4 1	0 4 4	0 2 8	0 1 1	0 1 2	0 4 4	0 1 4	0 2 2
General Body System																									
Tissue NOS			+																						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X													X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma													X			X	X	X	X			X			X
Interstitial cell, adenoma				X				X		X		X								X	X			X	
Hematopoietic System																									
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																	+		+		+	+			+
Lymph node, bronchial	M	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X														
Thymus	+	M	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma					X										X										
Squamous cell papilloma																				X					
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Osteosarcoma, metastatic, spleen											X														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	M	M	M	M	M	+	+	+	M	M	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																								X	
Osteosarcoma, metastatic, spleen											X														
Mediastinum, osteosarcoma, metastatic, spleen											X														
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	6 8 5	6 8 9	6 8 9	6 8 9	6 9 2	7 1 0	7 1 0	7 1 3	7 1 4	7 1 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 0 1	0 1 7	0 3 3	0 1 3	0 0 2	0 3 4	0 0 6	0 4 6	0 4 7	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 0	0 2 1	0 2 6	0 3 0	0 3 1	0 3 5	0 3 7	0 4 0	0 4 2	0 4 9	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Adenoma																X										3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	27
Interstitial cell, adenoma									X								X									9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node			+			+												+	+							9
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Fibroadenoma																	X								X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X													3
Squamous cell papilloma																		X								2
Subcutaneous tissue, fibroma																					X					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										1
Osteosarcoma, metastatic, spleen																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X												X					2
Alveolar/bronchiolar carcinoma												X														1
Carcinoma, metastatic, thyroid gland									X																	2
Osteosarcoma, metastatic, spleen																										1
Mediastinum, osteosarcoma, metastatic, spleen																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	3 5 4	3 9 1	4 7 9	4 9 7	5 2 8	5 4 7	5 5 3	5 7 0	5 7 4	5 8 4	5 9 0	6 0 2	6 0 8	6 0 9	6 1 8	6 2 3	6 3 0	6 3 9	6 4 0	6 4 0	6 4 4	6 5 2	6 5 3	6 6 1	6 6 8
Carcass ID Number	0 4 8	0 3 8	0 0 9	0 3 9	0 2 5	0 0 8	0 2 4	0 4 5	0 3 6	0 5 0	0 1 9	0 0 3	0 2 3	0 0 5	0 2 9	0 3 2	0 2 7	0 4 1	0 0 4	0 2 8	0 1 1	0 1 2	0 4 4	0 1 4	0 2 2
Special Senses System																									
Eye										+															
Zymbal's gland																									+
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X			X			X	X	X	X	X	X	X	X		X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	6 8 5	6 8 9	6 8 9	6 8 9	6 9 2	7 1 0	7 1 0	7 1 3	7 1 4	7 1 5	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	0 4 3	0 0 1	0 1 7	0 3 3	0 1 3	0 0 2	0 3 4	0 0 6	0 4 6	0 4 7	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 0	0 2 1	0 2 6	0 3 0	0 3 1	0 3 5	0 3 7	0 4 0	0 4 2	0 4 9	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X		X	X	X			X		X					X	X	X	X		X	X			27

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm

Number of Days on Study	2 4 4	3 0 8	3 5 2	4 1 6	5 1 8	5 3 8	5 4 9	5 6 0	5 8 2	5 8 4	5 8 4	5 9 6	6 0 0	6 0 1	6 0 7	6 1 5	6 1 7	6 1 9	6 2 6	6 3 1	6 3 4	6 3 7	6 3 9	6 4 0	6 5 4
Carcass ID Number	1 2 0 2	1 0 3	1 5 0	1 0 8	1 2 9	1 2 4	1 4 9	1 1 7	1 4 2	1 0 4	1 2 1	1 0 7	1 3 2	1 0 1	1 3 8	1 4 4	1 4 6	1 0 5	1 3 3	1 1 5	1 1 1	1 1 9	1 4 0	1 3 7	1 0 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	A	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	A	A	+	+	+	+
Intestine small, ileum	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X																X	
Histiocytic sarcoma														X											
Mesentery	+										+					+									
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Duct, carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign											X								X						
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																X	
Carcinoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X		X	X		X			X				X	X						X	X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
Follicular cell, carcinoma																									
General Body System																									
Peritoneum																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X						X		X			X				X				
Interstitial cell, adenoma									X		X				X								X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	6 6 8	6 7 1	6 9 2	6 9 3	6 9 5	7 0 7	7 1 3	7 1 4	7 1 8	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 2 3	1 3 5	1 4 1	1 2 5	1 2 7	1 3 0	1 4 3	1 3 9	1 2 8	1 1 6	1 4 5	1 0 2	1 0 6	1 1 0	1 1 2	1 1 3	1 1 4	1 1 8	1 2 0	1 2 6	1 3 1	1 3 4	1 3 6	1 4 7	1 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									3
Histiocytic sarcoma																										1
Mesentery						+														+						5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Duct, carcinoma												X														1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																	X									1
Pheochromocytoma benign					X			X	X			X					X		X		X			X		10
Bilateral, pheochromocytoma benign						X									X							X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X												X						4
Carcinoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X								X				X	X		X	X	X		X					18
Pars distalis, adenoma, multiple																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma									X	X		X							X		X					6
Follicular cell, carcinoma													X													1
General Body System																										
Peritoneum											+															1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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					10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	2 4 4	3 0 8	3 5 2	4 1 6	5 1 8	5 3 8	5 4 9	5 6 0	5 8 2	5 8 4	5 8 4	5 9 6	6 0 0	6 0 1	6 0 7	6 1 5	6 1 7	6 1 9	6 2 6	6 3 1	6 3 4	6 3 7	6 3 9	6 4 0	6 5 4
Carcass ID Number	1 2 2	1 0 3	1 5 0	1 0 8	1 2 9	1 2 4	1 4 9	1 1 7	1 4 2	1 0 4	1 2 1	1 1 7	1 3 2	1 0 1	1 3 8	1 4 4	1 4 6	1 0 5	1 3 3	1 1 5	1 1 1	1 1 9	1 4 0	1 3 7	1 0 9
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymph node						+					+											+			
Lymph node, bronchial	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	M
Histiocytic sarcoma														X											
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Thymus	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma														X											
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Fibroadenoma, multiple																									
Fibroma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																						X			
Squamous cell papilloma																									
Pinna, schwannoma benign																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Skeletal muscle														+											
Histiocytic sarcoma														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	A	M	+	+	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Histiocytic sarcoma														X											
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	6 6 8	6 7 1	6 9 2	6 9 3	6 9 5	7 0 7	7 1 3	7 1 4	7 1 8	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 2 3	1 3 5	1 4 1	1 2 5	1 2 7	1 3 0	1 4 3	1 3 9	1 2 8	1 1 6	1 4 5	1 0 2	1 0 6	1 1 0	1 1 2	1 1 3	1 1 4	1 1 8	1 2 0	1 2 6	1 3 1	1 3 4	1 3 6	1 4 7	1 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node				+				+							+						+		+			8
Lymph node, bronchial	+	+	M	+	+	M	M	+	M	M	+	+	M	+	M	+	+	M	M	+	+	+	M	+	+	34
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma																			X					X		2
Fibroadenoma, multiple														X												1
Fibroma						X																				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma									X																	2
Squamous cell papilloma														X												1
Pinna, schwannoma benign																						X				1
Subcutaneous tissue, fibroma							X																			1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma	X					X																				2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Skeletal muscle																										1
Histiocytic sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	2 4 4	3 0 8	3 5 2	4 1 6	5 1 8	5 3 8	5 4 9	5 6 0	5 8 2	5 8 4	5 8 4	5 9 6	6 0 0	6 0 1	6 0 7	6 1 5	6 1 7	6 1 9	6 2 6	6 3 1	6 3 4	6 3 7	6 3 9	6 4 0	6 5 4
Carcass ID Number	1 2 2	1 0 3	1 5 0	1 0 8	1 2 9	1 2 4	1 4 9	1 1 7	1 4 2	1 0 4	1 2 1	1 0 7	1 3 2	1 0 1	1 3 8	1 4 4	1 4 6	1 0 5	1 3 3	1 1 5	1 1 1	1 1 9	1 4 0	1 3 7	1 0 9
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Renal tubule, adenoma																	X		X						
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Leukemia mononuclear									X		X	X			X	X	X		X		X	X	X		X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	6 6 8	6 7 1	6 9 2	6 9 3	6 9 5	7 0 7	7 1 3	7 1 4	7 1 8	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	1 2 3	1 3 5	1 4 1	1 2 5	1 2 7	1 3 0	1 4 3	1 3 9	1 2 8	1 1 6	1 4 5	1 0 2	1 0 6	1 1 0	1 1 2	1 1 3	1 1 4	1 1 8	1 2 0	1 2 6	1 3 1	1 3 4	1 3 6	1 4 7	1 4 8	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma								X																		3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																X										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X		X	X			X	X	X	X	X	X			X		X			X		X	X	X	26
Mesothelioma malignant			X								X															2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm

Number of Days on Study	2 6 6	4 2 0	4 6 7	4 9 6	5 0 9	5 2 7	5 2 8	5 5 6	5 8 9	5 9 0	5 9 0	5 9 1	5 9 1	5 9 6	6 1 9	6 2 4	6 2 9	6 4 3	6 4 4	6 6 5	6 6 8	6 6 9	6 7 1	6 7 1	6 8 6
Carcass ID Number	2 3 8	2 3 7	2 1 9	2 0 4	2 0 9	2 4 3	2 4 2	2 0 3	2 3 3	2 3 2	2 2 3	2 2 8	2 4 9	2 2 5	2 3 2	2 3 0	2 1 7	2 4 5	2 2 6	2 1 6	2 2 9	2 2 4	2 0 1	2 3 5	2 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																	+								+
Lipoma																									X
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X													X		
Bilateral, pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X	X	X						X		X			X			X		X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X							X					
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma										X		X	X	X	X			X		X	X	X	X	X	X
Interstitial cell, adenoma		X			X				X							X	X								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	6 8 8	6 9 6	7 0 3	7 0 3	7 0 3	7 0 4	7 0 7	7 0 8	7 1 2	7 1 3	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 1 8	2 0 6	2 3 4	2 4 6	2 4 8	2 0 7	2 2 0	2 4 4	2 3 9	2 1 5	2 3 1	2 3 6	2 0 2	2 0 5	2 0 8	2 1 0	2 1 1	2 1 2	2 1 3	2 1 4	2 1 1	2 2 7	2 4 0	2 4 1	2 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery									+																	3
Lipoma																										1
Oral mucosa																	+									1
Pharyngeal, squamous cell papilloma																	X									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign															X								X	X	X	6
Bilateral, pheochromocytoma benign	X					X																				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X											X	X								4
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X						X		X	X		X					X		X	X			18
Pars distalis, adenoma, multiple																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X						3
Follicular cell, carcinoma															X											1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	32
Interstitial cell, adenoma								X				X									X					8

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	246	246	247	249	250	257	258	256	258	259	259	259	259	261	261	262	263	264	264	265	266	268	269	271	271	286
Carcass ID Number	238	237	239	204	209	243	242	203	233	222	233	228	249	225	232	230	217	245	266	216	229	244	211	255	270	250
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node											+			+					+							
Lymph node, bronchial	+	M	+	+	+	M	+	M	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																										
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	
Adenoma																		X								
Fibroadenoma																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																										
Keratoacanthoma																										
Squamous cell papilloma																										
Pinna, schwannoma malignant																			X							
Sebaceous gland, adenoma																									X	
Subcutaneous tissue, fibroma																										
Subcutaneous tissue, myxoma	X																									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Turbinate, chondroma																										
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant		X																								
Peripheral nerve																										+
Spinal cord													+													+
Respiratory System																										
Larynx	M	+	M	M	+	+	+	M	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																										
Special Senses System																										
Harderian gland																										+
Carcinoma																										X
Zymbal's gland																										
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X	
Renal tubule, carcinoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	6 8 8	6 9 6	7 0 3	7 0 3	7 0 3	7 0 4	7 0 7	7 0 8	7 1 2	7 1 3	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 1 8	2 0 6	2 3 4	2 4 6	2 4 8	2 0 7	2 2 0	2 4 4	2 3 9	2 1 5	2 3 1	2 3 6	2 0 2	2 0 5	2 0 8	2 1 0	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 7	2 4 0	2 4 1	2 4 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+					+			+	+							+				+					9
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	39
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymoma benign															X											1
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Fibroadenoma											X				X											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma	X																									1
Keratoacanthoma																	X						X			2
Squamous cell papilloma															X											1
Pinna, schwannoma malignant																										1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma	X														X				X							3
Subcutaneous tissue, myxoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Turbinate, chondroma																					X					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Peripheral nerve					+																					2
Spinal cord					+																					3
Respiratory System																										
Larynx	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma													X													1
Special Senses System																										
Harderian gland																										1
Carcinoma																										1
Zymbal's gland																				+						1
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																								X		2
Renal tubule, carcinoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	2	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	
	6	2	6	9	0	2	2	5	8	9	9	9	9	9	1	2	2	4	4	6	6	6	7	7	8
	6	0	7	6	9	7	8	6	9	0	0	1	1	6	9	4	9	3	4	5	8	9	1	1	6
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	3	3	1	0	0	4	4	0	3	2	2	2	4	2	3	3	1	4	2	1	2	2	0	3	5
	8	7	9	4	9	3	2	3	3	2	3	8	9	5	2	0	7	5	6	6	9	4	1	5	0
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X			X	X	X	X	X	X	X				X	X	X	X				
Mesothelioma malignant						X																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	6 8 8	6 9 6	7 0 3	7 0 3	7 0 3	7 0 4	7 0 7	7 0 8	7 1 2	7 1 3	7 2 0	7 2 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 1 8	2 0 6	2 3 4	2 4 6	2 4 8	2 0 7	2 2 0	2 4 4	2 3 9	2 1 5	2 3 1	2 3 6	2 0 2	2 0 5	2 0 8	2 1 0	2 1 1	2 1 2	2 1 3	2 1 4	2 2 1	2 2 7	2 4 0	2 4 1	2 4 7	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X	X	X	X	X	X			X	X		X	X			X	X	X		32
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm

Number of Days on Study	3 7 7	3 8 3	3 9 3	4 8 3	5 0 0	5 0 7	5 3 8	5 3 9	5 4 6	5 4 7	5 5 5	5 6 3	5 6 7	5 6 9	5 7 2	5 8 4	5 8 6	5 8 7	5 8 7	5 8 7	5 8 8	5 9 0	5 9 0	5 9 1	5 9 4
Carcass ID Number	3 4 4	3 4 7	3 2 9	3 2 7	3 4 3	3 3 6	3 1 5	3 5 0	3 1 6	3 0 9	3 0 8	3 2 1	3 0 4	3 2 6	3 1 7	3 2 4	3 1 3	3 1 1	3 1 9	3 2 5	3 0 6	3 1 4	3 3 7	3 4 5	3 4 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	A	+	+	+	A	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	A	A	A	+	+	+	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	A	A	A	A	+	+	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery													+					+					+		
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Pheochromocytoma malignant						X												X							
Pheochromocytoma benign										X									X		X				
Bilateral, pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma	X						X					X	X					X				X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Bilateral, adenoma					X				X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X
Interstitial cell, adenoma				X												X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	5 9 3 6	5 9 4 7	6 1 8 6	6 2 4 6	6 2 4 7	6 4 0 1	6 4 0 3	6 4 0 5	6 5 4 1	6 5 4 2	6 6 2 1	6 6 2 3	6 6 3 5	6 6 3 8	6 7 0 2	6 7 2 1	6 7 3 0	6 8 2 3	6 8 3 1	6 9 1 6	6 9 4 6	7 0 4 8	7 0 2 1	7 0 3 8	7 1 0 7	7 3 0 9	7 3 0 0	7 3 1 0	
Carcass ID Number	3 3 3 3	3 4 1 1	3 1 8 8	3 3 4 4	3 3 9 9	3 4 0 0	3 0 5 5	3 4 2 2	3 2 2 0	3 2 2 2	3 2 3 8	3 3 0 2	3 3 5 5	3 0 2 2	3 3 1 1	3 2 1 0	3 1 4 3	3 2 3 3	3 1 2 2	3 4 6 6	3 4 4 8	3 0 1 1	3 3 8 8	3 0 0 7	3 0 1 3	3 1 0 4	Total Tissues/ Tumors
Alimentary System																													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	48
Intestine large, cecum	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	A	+	A	+	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	34
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery																													3
Oral mucosa	+																												1
Pharyngeal, squamous cell papilloma	X																												1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																													
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																													2
Pheochromocytoma benign			X					X												X	X					X	X	9
Bilateral, pheochromocytoma benign																	X								X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X	X									X										X	4
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M			46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			45
Pars distalis, adenoma		X		X		X			X	X		X	X					X					X		X				18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
C-cell, adenoma													X										X						2
Follicular cell, carcinoma											X																		1
General Body System																													
None																													
Genital System																													
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X								X				2
Bilateral, adenoma																													2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	X	X	X	X	40
Interstitial cell, adenoma									X	X																			4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	3 7 7	3 8 3	3 9 3	4 8 3	5 0 0	5 0 7	5 3 8	5 3 9	5 4 6	5 4 7	5 5 5	5 6 3	5 6 7	5 6 9	5 7 2	5 8 4	5 8 6	5 8 7	5 8 7	5 8 7	5 8 8	5 9 0	5 9 0	5 9 1	5 9 4
Carcass ID Number	3 4 4	3 4 7	3 2 9	3 2 7	3 4 3	3 3 6	3 1 5	3 5 0	3 1 6	3 0 9	3 0 8	3 2 1	3 0 4	3 2 6	3 1 7	3 2 4	3 1 3	3 1 1	3 1 9	3 2 5	3 0 6	3 1 4	3 3 7	3 4 5	3 4 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+		+			+		+				+		+					+
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	M	+	+	M	M	M	M	M	M	+	+	+	M	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant					X																				
Respiratory System																									
Larynx	M	+	+	+	M	+	M	+	+	+	+	M	M	M	+	+	M	+	+	M	M	+	M	M	M
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																			X						
Renal tubule, carcinoma																		X							
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X				X		X			X								X					X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	5 9 6	5 9 7	6 1 6	6 2 6	6 2 7	6 4 1	6 4 3	6 4 5	6 5 1	6 5 2	6 6 1	6 6 3	6 6 5	6 6 8	6 7 2	6 7 9	6 8 0	6 8 1	6 9 6	6 9 6	7 0 2	7 0 9	7 1 9	7 3 4	7 3 4	
Carcass ID Number	3 3 3	3 4 1	3 1 8	3 3 4	3 3 9	3 4 0	3 0 5	3 4 2	3 2 0	3 2 2	3 2 8	3 3 2	3 3 5	3 0 2	3 3 1	3 3 0	3 2 3	3 1 2	3 4 6	3 4 8	3 0 1	3 3 8	3 0 7	3 0 4	3 1 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+			+			+						+				+					+		14
Lymph node, bronchial	M	+	+	M	+	M	+	M	M	M	M	M	M	+	+	M	+	M	M	+	+	+	+	+	M	+	28
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																							X			1
Keratoacanthoma															X										X	2
Subcutaneous tissue, lipoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																						+				1
Sarcoma																						X				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Respiratory System																										
Larynx	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		35
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																										
Zymbal's gland																						+				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Renal tubule, adenoma			X									X													X		4
Renal tubule, carcinoma		X							X																		3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear															X										X		9

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	13/50 (26%)	13/50 (26%)	9/49 (18%)	12/48 (25%)
Adjusted rate[b]	48.8%	62.0%	42.6%	100.0%
Terminal rate[c]	4/15 (27%)	7/14 (50%)	4/13 (31%)	2/2 (100%)
First incidence (days)	584	584	590	546
Life table test[d]	P = 0.003	P = 0.545	P = 0.279N	P = 0.014
Logistic regression test[d]	P = 0.211	P = 0.552	P = 0.233N	P = 0.307
Cochran-Armitage test[d]	P = 0.516N			
Fisher exact test[d]		P = 0.590N	P = 0.251N	P = 0.547N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	13/50 (26%)	13/50 (26%)	9/49 (18%)	14/48 (29%)
Adjusted rate	48.8%	62.0%	42.6%	100.0%
Terminal rate	4/15 (27%)	7/14 (50%)	4/13 (31%)	2/2 (100%)
First incidence (days)	584	584	590	507
Life table test	P < 0.001	P = 0.545	P = 0.279N	P = 0.005
Logistic regression test	P = 0.106	P = 0.552	P = 0.233N	P = 0.214
Cochran-Armitage test	P = 0.379			
Fisher exact test		P = 0.590N	P = 0.251N	P = 0.450
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rate	0.0%	11.2%	11.0%	56.9%
Terminal rate	0/15 (0%)	0/14 (0%)	1/13 (8%)	1/2 (50%)
First incidence (days)	—[e]	617	671	587
Life table test	P = 0.006	P = 0.120	P = 0.236	P = 0.008
Logistic regression test	P = 0.064	P = 0.119	P = 0.240	P = 0.037
Cochran-Armitage test	P = 0.109			
Fisher exact test		P = 0.121	P = 0.247	P = 0.059
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	3/50 (6%)	2/50 (4%)	7/50 (14%)	17/50 (34%)
Adjusted rate	13.4%	14.3%	39.7%	88.8%
Terminal rate	0/15 (0%)	2/14 (14%)	4/13 (31%)	1/2 (50%)
First incidence (days)	685	734 (T)	671	572
Life table test	P < 0.001	P = 0.519N	P = 0.144	P < 0.001
Logistic regression test	P < 0.001	P = 0.516N	P = 0.159	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.500N	P = 0.159	P < 0.001
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	3/50 (6%)	5/50 (10%)	7/50 (14%)	20/50 (40%)
Adjusted rate	13.4%	23.9%	39.7%	100.0%
Terminal rate	0/15 (0%)	2/14 (14%)	4/13 (31%)	2/2 (100%)
First incidence (days)	685	617	671	572
Life table test	P < 0.001	P = 0.343	P = 0.144	P < 0.001
Logistic regression test	P < 0.001	P = 0.337	P = 0.159	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.357	P = 0.159	P < 0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Kidney (Renal Tubule): Carcinoma (Single Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	7.7%	12.5%
Terminal rate	0/15 (0%)	0/14 (0%)	1/13 (8%)	0/2 (0%)
First incidence (days)	—	—	734 (T)	587
Life table test	P = 0.002	—[f]	P = 0.471	P = 0.063
Logistic regression test	P = 0.018	—	P = 0.471	P = 0.129
Cochran-Armitage test	P = 0.021			
Fisher exact test		—	P = 0.500	P = 0.121
Kidney (Renal Tubule): Carcinoma (Step Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	7.7%	12.5%
Terminal rate	0/15 (0%)	0/14 (0%)	1/13 (8%)	0/2 (0%)
First incidence (days)	—	—	734 (T)	587
Life table test	P = 0.002	—	P = 0.471	P = 0.063
Logistic regression test	P = 0.018	—	P = 0.471	P = 0.129
Cochran-Armitage test	P = 0.021			
Fisher exact test		—	P = 0.500	P = 0.121
Kidney (Renal Tubule): Carcinoma (Single and Step Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	7.7%	12.5%
Terminal rate	0/15 (0%)	0/14 (0%)	1/13 (8%)	0/2 (0%)
First incidence (days)	—	—	734 (T)	587
Life table test	P = 0.002	—	P = 0.471	P = 0.063
Logistic regression test	P = 0.018	—	P = 0.471	P = 0.129
Cochran-Armitage test	P = 0.021			
Fisher exact test		—	P = 0.500	P = 0.121
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted rate	0.0%	11.2%	18.4%	62.4%
Terminal rate	0/15 (0%)	0/14 (0%)	2/13 (15%)	1/2 (50%)
First incidence (days)	—	617	671	587
Life table test	P < 0.001	P = 0.120	P = 0.111	P < 0.001
Logistic regression test	P = 0.003	P = 0.119	P = 0.121	P = 0.006
Cochran-Armitage test	P = 0.007			
Fisher exact test		P = 0.121	P = 0.121	P = 0.006
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections)				
Overall rate	3/50 (6%)	2/50 (4%)	8/50 (16%)	18/50 (36%)
Adjusted rate	13.4%	14.3%	46.4%	89.1%
Terminal rate	0/15 (0%)	2/14 (14%)	5/13 (38%)	1/2 (50%)
First incidence (days)	685	734 (T)	671	572
Life table test	P < 0.001	P = 0.519N	P = 0.087	P < 0.001
Logistic regression test	P < 0.001	P = 0.516N	P = 0.098	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.500N	P = 0.100	P < 0.001

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	3/50 (6%)	5/50 (10%)	8/50 (16%)	21/50 (42%)
Adjusted rate	13.4%	23.9%	46.4%	100.0%
Terminal rate	0/15 (0%)	2/14 (14%)	5/13 (38%)	2/2 (100%)
First incidence (days)	685	617	671	572
Life table test	P < 0.001	P = 0.343	P = 0.087	P < 0.001
Logistic regression test	P < 0.001	P = 0.337	P = 0.098	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.357	P = 0.100	P < 0.001
Liver: Hepatocellular Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/49 (0%)
Adjusted rate	0.0%	9.7%	0.0%	0.0%
Terminal rate	0/15 (0%)	0/14 (0%)	0/13 (0%)	0/2 (0%)
First incidence (days)	—	560	—	—
Life table test	P = 0.326N	P = 0.112	—	—
Logistic regression test	P = 0.246N	P = 0.125	—	—
Cochran-Armitage test	P = 0.259N			
Fisher exact test		P = 0.121	—	—
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	18.4%	5.3%	0.0%	10.0%
Terminal rate	2/15 (13%)	0/14 (0%)	0/13 (0%)	0/2 (0%)
First incidence (days)	714	713	—	679
Life table test	P = 0.643	P = 0.309N	P = 0.146N	P = 0.593
Logistic regression test	P = 0.635N	P = 0.310N	P = 0.119N	P = 0.740N
Cochran-Armitage test	P = 0.339N			
Fisher exact test		P = 0.309N	P = 0.121N	P = 0.309N
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	13.3%	21.4%	13.8%	0.0%
Terminal rate	2/15 (13%)	3/14 (21%)	1/13 (8%)	0/2 (0%)
First incidence (days)	734 (T)	734 (T)	720	—
Life table test	P = 0.547N	P = 0.467	P = 0.657	P = 0.726N
Logistic regression test	P = 0.503N	P = 0.467	P = 0.681	P = 0.726N
Cochran-Armitage test	P = 0.116N			
Fisher exact test		P = 0.500	P = 0.691N	P = 0.247N
Mammary Gland: Fibroma, Fibroadenoma, or Adenoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	0/50 (0%)
Adjusted rate	13.3%	27.1%	16.5%	0.0%
Terminal rate	2/15 (13%)	3/14 (21%)	1/13 (8%)	0/2 (0%)
First incidence (days)	734 (T)	549	643	—
Life table test	P = 0.382N	P = 0.193	P = 0.470	P = 0.726N
Logistic regression test	P = 0.180N	P = 0.199	P = 0.507	P = 0.726N
Cochran-Armitage test	P = 0.073N			
Fisher exact test		P = 0.218	P = 0.500	P = 0.247N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Oral Cavity (Oral Mucosa and Tongue): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted rate	12.6%	0.0%	7.7%	4.0%
Terminal rate	1/15 (7%)	0/14 (0%)	1/13 (8%)	0/2 (0%)
First incidence (days)	570	—	734 (T)	596
Life table test	P = 0.618	P = 0.132N	P = 0.335N	P = 0.639N
Logistic regression test	P = 0.505N	P = 0.124N	P = 0.303N	P = 0.348N
Cochran-Armitage test	P = 0.442N			
Fisher exact test		P = 0.121N	P = 0.309N	P = 0.309N
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	16.0%	17.5%	22.5%	60.5%
Terminal rate	1/15 (7%)	1/14 (7%)	2/13 (15%)	1/2 (50%)
First incidence (days)	692	560	671	645
Life table test	P = 0.033	P = 0.492	P = 0.477	P = 0.043
Logistic regression test	P = 0.220	P = 0.483	P = 0.509	P = 0.163
Cochran-Armitage test	P = 0.493			
Fisher exact test		P = 0.500	P = 0.500	P = 0.500
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted rate	23.3%	23.9%	22.5%	60.5%
Terminal rate	1/15 (7%)	2/14 (14%)	2/13 (15%)	1/2 (50%)
First incidence (days)	590	560	671	645
Life table test	P = 0.116	P = 0.617	P = 0.523N	P = 0.152
Logistic regression test	P = 0.464	P = 0.612	P = 0.492N	P = 0.462
Cochran-Armitage test	P = 0.429N			
Fisher exact test		P = 0.630N	P = 0.500N	P = 0.500N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	25/49 (51%)	19/50 (38%)	19/50 (38%)	18/45 (40%)
Adjusted rate	79.7%	66.7%	65.8%	82.7%
Terminal rate	9/14 (64%)	7/14 (50%)	6/13 (46%)	1/2 (50%)
First incidence (days)	391	518	420	377
Life table test	P = 0.034	P = 0.222N	P = 0.237N	P = 0.068
Logistic regression test	P = 0.355N	P = 0.147N	P = 0.135N	P = 0.234N
Cochran-Armitage test	P = 0.314N			
Fisher exact test		P = 0.135N	P = 0.135N	P = 0.194N
Preputial Gland: Adenoma				
Overall rate	3/49 (6%)	1/50 (2%)	1/49 (2%)	4/50 (8%)
Adjusted rate	12.5%	2.3%	7.7%	42.7%
Terminal rate	1/14 (7%)	0/14 (0%)	1/13 (8%)	0/2 (0%)
First incidence (days)	574	560	734 (T)	500
Life table test	P = 0.048	P = 0.318N	P = 0.314N	P = 0.172
Logistic regression test	P = 0.228	P = 0.291N	P = 0.302N	P = 0.502
Cochran-Armitage test	P = 0.227			
Fisher exact test		P = 0.301N	P = 0.309N	P = 0.511

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	11.2%	9.1%	15.4%	54.5%
Terminal rate	1/15 (7%)	0/14 (0%)	2/13 (15%)	1/2 (50%)
First incidence (days)	528	637	734 (T)	672
Life table test	P = 0.306	P = 0.516N	P = 0.543N	P = 0.462
Logistic regression test	P = 0.608	P = 0.501N	P = 0.500N	P = 0.606N
Cochran-Armitage test	P = 0.491N			
Fisher exact test		P = 0.500N	P = 0.500N	P = 0.500N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	5/50 (10%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	20.1%	15.6%	23.1%	54.5%
Terminal rate	2/15 (13%)	1/14 (7%)	3/13 (23%)	1/2 (50%)
First incidence (days)	528	637	734 (T)	672
Life table test	P = 0.483	P = 0.393N	P = 0.407N	P = 0.646
Logistic regression test	P = 0.422N	P = 0.368N	P = 0.353N	P = 0.342N
Cochran-Armitage test	P = 0.225N			
Fisher exact test		P = 0.357N	P = 0.357N	P = 0.218N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted	20.1%	15.6%	26.2%	69.7%
Terminal	2/15 (13%)	1/14 (7%)	3/13 (23%)	1/2 (50%)
First incidence (days)	528	637	688	672
Life table	P = 0.183	P = 0.393N	P = 0.548N	P = 0.358
Logistic regression	P = 0.535	P = 0.368N	P = 0.497N	P = 0.575N
Cochran-Armitage	P = 0.389N			
Fisher exact		P = 0.357N	P = 0.500N	P = 0.357N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.7%	5.3%	18.8%	0.0%
Terminal rate	1/15 (7%)	0/14 (0%)	2/13 (15%)	0/2 (0%)
First incidence (days)	734 (T)	713	688	—
Life table test	P = 0.624	P = 0.759	P = 0.269	P = 0.882N
Logistic regression test	P = 0.690N	P = 0.759	P = 0.302	P = 0.882N
Cochran-Armitage test	P = 0.339N			
Fisher exact test		P = 0.753N	P = 0.309	P = 0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	10.9%	0.0%	0.0%
Terminal rate	0/15 (0%)	0/14 (0%)	0/13 (0%)	0/2 (0%)
First incidence (days)	—	560	—	—
Life table test	P = 0.380N	P = 0.122	—	—
Logistic regression test	P = 0.259N	P = 0.120	—	—
Cochran-Armitage test	P = 0.255N			
Fisher exact test		P = 0.121	—	—

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Skin (Subcutaneous Tissue): Fibroma, Myxoma, Fibrosarcoma, or Sarcoma				
Overall rate	1/50 (2%)	4/50 (8%)	4/50 (8%)	0/50 (0%)
Adjusted rate	6.7%	15.6%	20.4%	0.0%
Terminal rate	1/15 (7%)	0/14 (0%)	2/13 (15%)	0/2 (0%)
First incidence (days)	734 (T)	560	266	—
Life table test	P = 0.487N	P = 0.182	P = 0.157	P = 0.882N
Logistic regression test	P = 0.323N	P = 0.171	P = 0.181	P = 0.882N
Cochran-Armitage test	P = 0.155N			
Fisher exact test		P = 0.181	P = 0.181	P = 0.500N
Testes: Bilateral Adenoma				
Overall rate	27/50 (54%)	23/50 (46%)	32/50 (64%)	40/50 (80%)
Adjusted rate	96.0%	91.0%	96.5%	100.0%
Terminal rate	14/15 (93%)	12/14 (86%)	12/13 (92%)	2/2 (100%)
First incidence (days)	608	538	590	500
Life table test	P < 0.001	P = 0.364N	P = 0.185	P < 0.001
Logistic regression test	P < 0.001	P = 0.313N	P = 0.177	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		P = 0.274N	P = 0.208	P = 0.005
Testes: Adenoma				
Overall rate	36/50 (72%)	33/50 (66%)	40/50 (80%)	44/50 (88%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	15/15 (100%)	14/14 (100%)	13/13 (100%)	2/2 (100%)
First incidence (days)	497	538	420	483
Life table test	P < 0.001	P = 0.480N	P = 0.259	P < 0.001
Logistic regression test	P < 0.001	P = 0.404N	P = 0.194	P = 0.001
Cochran-Armitage test	P = 0.010			
Fisher exact test		P = 0.333N	P = 0.241	P = 0.039
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	6/49 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	20.0%	32.7%	13.0%	30.8%
Terminal rate	3/15 (20%)	3/14 (21%)	1/13 (8%)	0/2 (0%)
First incidence (days)	734 (T)	617	591	665
Life table test	P = 0.366	P = 0.223	P = 0.633	P = 0.208
Logistic regression test	P = 0.539N	P = 0.217	P = 0.659N	P = 0.390
Cochran-Armitage test	P = 0.217N			
Fisher exact test		P = 0.233	P = 0.661N	P = 0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/50 (10%)	6/49 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	27.5%	32.7%	13.0%	30.8%
Terminal rate	3/15 (20%)	3/14 (21%)	1/13 (8%)	0/2 (0%)
First incidence (days)	661	617	591	665
Life table test	P = 0.553	P = 0.481	P = 0.384N	P = 0.444
Logistic regression test	P = 0.342N	P = 0.474	P = 0.349N	P = 0.676N
Cochran-Armitage test	P = 0.112N			
Fisher exact test		P = 0.486	P = 0.357N	P = 0.218N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	26/50 (52%)	32/50 (64%)	9/50 (18%)
Adjusted rate	74.7%	79.3%	83.1%	62.2%
Terminal rate	7/15 (47%)	8/14 (57%)	7/13 (54%)	1/2 (50%)
First incidence (days)	570	582	496	383
Life table test	P = 0.412N	P = 0.543	P = 0.264	P = 0.287N
Logistic regression test	P < 0.001N	P = 0.555N	P = 0.166	P < 0.001N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.500N	P = 0.208	P < 0.001N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	44/50 (88%)	48/50 (96%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	15/15 (100%)	14/14 (100%)	13/13 (100%)	2/2 (100%)
First incidence (days)	391	518	266	377
Life table test	P < 0.001	P = 0.452N	P = 0.475	P < 0.001
Logistic regression test	P = 0.184	P = 0.205N	P = 0.667	P = 0.586
Cochran-Armitage test	P = 0.296			
Fisher exact test		P = 0.134N	P = 0.691N	P = 0.691N
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	32/50 (64%)	37/50 (74%)	17/50 (34%)
Adjusted rate	83.6%	85.7%	89.6%	85.3%
Terminal rate	9/15 (60%)	9/14 (64%)	9/13 (69%)	1/2 (50%)
First incidence (days)	497	560	420	383
Life table test	P = 0.225	P = 0.532	P = 0.310	P = 0.368
Logistic regression test	P = 0.001N	P = 0.551N	P = 0.247	P = 0.003N
Cochran-Armitage test	P < 0.001N			
Fisher exact test		P = 0.500N	P = 0.257	P = 0.001N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	45/50 (90%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	15/15 (100%)	14/14 (100%)	13/13 (100%)	2/2 (100%)
First incidence (days)	391	518	266	377
Life table test	P < 0.001	P = 0.454N	P = 0.430	P < 0.001
Logistic regression test	P = 0.059	P = 0.151N	P = 0.349	—
Cochran-Armitage test	P = 0.081			
Fisher exact test		P = 0.102N	P = 0.500	P = 0.500

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposure group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at IIT Research Institute			
Isobutyl Nitrite	0/45	0/45	0/45
Overall Historical Incidence			
Total	6/652 (0.9%)	0/652 (0%)	6/652 (0.9%)
Standard deviation	1.3%		1.3%
Range	0%-4%		0%-4%

[a] Data as of 12 May 1995

TABLE A4b
Historical Incidence of Testicular Adenoma in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at IIT Research Institute	
Isobutyl Nitrite	31/46
Overall Historical Incidence	
Total	450/655 (68.7%)
Standard deviation	8.7%
Range	54%-83%

[a] Data as of 12 May 1995

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	28	20	26	26
Natural deaths	7	16	11	22
Survivors				
Terminal sacrifice	15	14	13	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(48)	(48)	(48)
Hemorrhage		1 (2%)		
Inflammation		1 (2%)		
Mineralization	1 (2%)	1 (2%)		1 (2%)
Intestine large, rectum	(48)	(49)	(48)	(48)
Thrombosis			1 (2%)	
Intestine large, cecum	(46)	(44)	(46)	(39)
Inflammation	1 (2%)	2 (5%)		1 (3%)
Mineralization				1 (3%)
Necrosis		1 (2%)		
Ulcer	1 (2%)			
Intestine small, duodenum	(48)	(48)	(50)	(50)
Mineralization	1 (2%)			
Necrosis			1 (2%)	
Intestine small, jejunum	(42)	(39)	(44)	(34)
Inflammation				1 (3%)
Intestine small, ileum	(45)	(44)	(45)	(37)
Inflammation				1 (3%)
Liver	(50)	(50)	(50)	(49)
Angiectasis			2 (4%)	1 (2%)
Basophilic focus	6 (12%)	5 (10%)	2 (4%)	4 (8%)
Clear cell focus	2 (4%)	3 (6%)	3 (6%)	
Cyst		1 (2%)		
Degeneration	1 (2%)			
Degeneration, cystic	15 (30%)	12 (24%)	19 (38%)	30 (61%)
Eosinophilic focus	5 (10%)	11 (22%)	4 (8%)	9 (18%)
Fibrosis		3 (6%)		
Hemorrhage		2 (4%)		
Hepatodiaphragmatic nodule		1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Inflammation, chronic active		1 (2%)		
Mineralization				1 (2%)
Mixed cell focus	1 (2%)	2 (4%)		
Necrosis	2 (4%)	4 (8%)		8 (16%)
Pigmentation	1 (2%)			
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	8 (16%)	10 (20%)	7 (14%)	4 (8%)
Bile duct, hyperplasia				1 (2%)
Bile duct, inflammation, suppurative		1 (2%)		
Kupffer cell, hyperplasia			1 (2%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Alimentary System (continued)				
Mesentery	(4)	(5)	(3)	(3)
Inflammation		1 (20%)		
Fat, necrosis	3 (75%)	4 (80%)	2 (67%)	3 (100%)
Pancreas	(50)	(49)	(50)	(50)
Inflammation		2 (4%)	1 (2%)	1 (2%)
Acinus, atrophy	24 (48%)	21 (43%)	20 (40%)	18 (36%)
Acinus, hyperplasia	4 (8%)		1 (2%)	
Artery, degeneration		1 (2%)	1 (2%)	
Artery, inflammation		1 (2%)		
Artery, mineralization		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)		1 (2%)	
Hyperplasia	8 (16%)	5 (10%)	8 (16%)	8 (16%)
Inflammation	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Mineralization	2 (4%)	1 (2%)	1 (2%)	5 (10%)
Ulcer	9 (18%)	9 (18%)	9 (18%)	10 (20%)
Stomach, glandular	(50)	(49)	(50)	(50)
Degeneration			1 (2%)	
Degeneration, cystic				1 (2%)
Inflammation	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Mineralization	4 (8%)	4 (8%)	3 (6%)	18 (36%)
Necrosis	5 (10%)	2 (4%)	2 (4%)	
Ulcer		2 (4%)		2 (4%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Aorta, inflammation			1 (2%)	1 (2%)
Aorta, mineralization	2 (4%)	2 (4%)	4 (8%)	14 (28%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	26 (52%)	21 (42%)	15 (30%)	30 (60%)
Inflammation			1 (2%)	
Mineralization	2 (4%)	1 (2%)		7 (14%)
Atrium, thrombosis	5 (10%)	7 (14%)	7 (14%)	
Valve, fibrosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Cytoplasmic alteration		1 (2%)		
Degeneration			1 (2%)	
Degeneration, cystic	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Hyperplasia	1 (2%)		1 (2%)	2 (4%)
Hypertrophy				1 (2%)
Necrosis			1 (2%)	2 (4%)
Pigmentation	1 (2%)			
Vacuolization cytoplasmic	13 (26%)	18 (36%)	16 (32%)	11 (22%)
Bilateral, atrophy	1 (2%)			
Capsule, inflammation				1 (2%)
Adrenal medulla	(50)	(50)	(49)	(48)
Hyperplasia	10 (20%)	7 (14%)	13 (27%)	8 (17%)
Necrosis				1 (2%)
Bilateral, hyperplasia	2 (4%)	2 (4%)	1 (2%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	5 (10%)	4 (8%)	
Parathyroid gland	(45)	(46)	(46)	(46)
Fibrosis			1 (2%)	
Hyperplasia	12 (27%)	6 (13%)	16 (35%)	35 (76%)
Pituitary gland	(49)	(50)	(50)	(45)
Pars distalis, angiectasis	5 (10%)	11 (22%)	5 (10%)	4 (9%)
Pars distalis, cyst	1 (2%)	6 (12%)	5 (10%)	4 (9%)
Pars distalis, degeneration			1 (2%)	
Pars distalis, hemorrhage		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	12 (24%)	11 (22%)	12 (24%)	12 (27%)
Pars distalis, necrosis			1 (2%)	
Pars distalis, pigmentation	1 (2%)		2 (4%)	
Pars intermedia, angiectasis	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
Cyst		1 (2%)		
C-cell, hyperplasia	6 (12%)	5 (10%)	5 (10%)	
Follicle, cyst	1 (2%)	1 (2%)		2 (4%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm		1 (2%)	1 (2%)	
Inflammation		1 (2%)	1 (2%)	1 (2%)
Mineralization				1 (2%)
Preputial gland	(49)	(50)	(49)	(50)
Atrophy			1 (2%)	
Hyperplasia	2 (4%)	2 (4%)		1 (2%)
Inflammation	19 (39%)	7 (14%)	8 (16%)	10 (20%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation	11 (22%)	29 (58%)	22 (44%)	25 (50%)
Seminal vesicle	(49)	(49)	(50)	(50)
Inflammation		1 (2%)	1 (2%)	
Mineralization	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Atrophy	10 (20%)	7 (14%)	10 (20%)	6 (12%)
Degeneration		1 (2%)		1 (2%)
Hemorrhage	1 (2%)			
Mineralization				2 (4%)
Arteriole, inflammation		1 (2%)	1 (2%)	
Bilateral, atrophy	9 (18%)	7 (14%)	5 (10%)	4 (8%)
Bilateral, necrosis			1 (2%)	
Interstitial cell, hyperplasia	14 (28%)	19 (38%)	12 (24%)	8 (16%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System				
Bone marrow	(49)	(49)	(50)	(50)
Atrophy			1 (2%)	1 (2%)
Hemorrhage	1 (2%)		2 (4%)	4 (8%)
Hyperplasia	7 (14%)	16 (33%)	9 (18%)	19 (38%)
Inflammation		1 (2%)		
Myelofibrosis	3 (6%)			5 (10%)
Myeloid cell, atrophy	1 (2%)			
Lymph node	(9)	(8)	(9)	(14)
Hemorrhage			1 (11%)	
Lumbar, hemorrhage		1 (13%)		
Lumbar, hyperplasia, plasma cell		1 (13%)		
Pancreatic, fibrosis			1 (11%)	
Pancreatic, pigmentation			1 (11%)	
Renal, ectasia			2 (22%)	1 (7%)
Renal, hemorrhage			1 (11%)	8 (57%)
Renal, hyperplasia, lymphoid				1 (7%)
Renal, hyperplasia, plasma cell			1 (11%)	1 (7%)
Renal, infiltration cellular, histiocyte		1 (13%)		
Renal, pigmentation			1 (11%)	2 (14%)
Lymph node, bronchial	(44)	(34)	(39)	(28)
Ectasia			1 (3%)	
Hemorrhage	7 (16%)	4 (12%)	4 (10%)	7 (25%)
Infiltration cellular, histiocyte			2 (5%)	
Pigmentation	3 (7%)	3 (9%)		5 (18%)
Lymph node, mandibular	(47)	(48)	(49)	(50)
Atrophy		1 (2%)		
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia, plasma cell	4 (9%)	1 (2%)	1 (2%)	4 (8%)
Inflammation			1 (2%)	
Pigmentation	1 (2%)			
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		
Ectasia			1 (2%)	
Hemorrhage	3 (6%)	5 (10%)	4 (8%)	8 (16%)
Inflammation			1 (2%)	1 (2%)
Lymph node, mediastinal	(48)	(48)	(50)	(47)
Edema	1 (2%)	1 (2%)		3 (6%)
Hemorrhage	12 (25%)	10 (21%)	10 (20%)	17 (36%)
Hyperplasia, plasma cell	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte	2 (4%)	1 (2%)		1 (2%)
Inflammation			1 (2%)	
Pigmentation	9 (19%)	8 (17%)	7 (14%)	7 (15%)
Spleen	(50)	(49)	(50)	(50)
Atrophy				2 (4%)
Congestion	1 (2%)	1 (2%)		
Depletion cellular		2 (4%)	3 (6%)	4 (8%)
Fibrosis	3 (6%)	1 (2%)	4 (8%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Inflammation, chronic			1 (2%)	
Necrosis	2 (4%)			2 (4%)
Pigmentation		1 (2%)		
Red pulp, depletion cellular			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System (continued)				
Thymus	(46)	(44)	(46)	(44)
Cyst				1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(46)	(47)	(46)	(49)
Fibrosis			1 (2%)	
Galactocele	11 (24%)	11 (23%)	11 (24%)	9 (18%)
Hyperplasia	3 (7%)	3 (6%)	4 (9%)	3 (6%)
Inflammation	1 (2%)	2 (4%)	1 (2%)	
Mineralization				1 (2%)
Pigmentation	1 (2%)	4 (9%)	2 (4%)	6 (12%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)	4 (8%)	2 (4%)	
Hyperkeratosis	1 (2%)			1 (2%)
Inflammation				1 (2%)
Inflammation, granulomatous		1 (2%)		
Epidermis, hyperplasia			1 (2%)	
Subcutaneous tissue, inflammation		2 (4%)		
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	1 (2%)	5 (10%)	9 (18%)
Hyperostosis			2 (4%)	
Turbinate, hyperostosis	1 (2%)	1 (2%)		1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Hydrocephalus	1 (2%)	2 (4%)	1 (2%)	
Mineralization			1 (2%)	
Necrosis	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Respiratory System				
Larynx	(40)	(44)	(41)	(35)
Foreign body			1 (2%)	
Infiltration cellular, lymphocyte	1 (3%)	1 (2%)	1 (2%)	1 (3%)
Inflammation	1 (3%)	3 (7%)	3 (7%)	1 (3%)
Necrosis		1 (2%)		
Respiratory epithelium, hyperplasia	1 (3%)	4 (9%)	1 (2%)	1 (3%)
Respiratory epithelium, metaplasia, squamous	1 (3%)	1 (2%)	1 (2%)	2 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Respiratory System (continued)				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)	2 (4%)		6 (12%)
Edema	1 (2%)			6 (12%)
Fibrosis			1 (2%)	1 (2%)
Foreign body			1 (2%)	
Hemorrhage		2 (4%)	1 (2%)	8 (16%)
Infiltration cellular, histiocyte	2 (4%)	1 (2%)		
Inflammation, acute		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)	3 (6%)	2 (4%)	7 (14%)
Inflammation, granulomatous	1 (2%)	1 (2%)		
Mineralization	1 (2%)	1 (2%)		3 (6%)
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Artery, mineralization				1 (2%)
Goblet cell, hyperplasia			1 (2%)	
Interstitium, fibrosis		1 (2%)		
Interstitium, inflammation				1 (2%)
Nose	(49)	(49)	(50)	(50)
Angiectasis			1 (2%)	
Congestion				1 (2%)
Foreign body	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation	8 (16%)	8 (16%)	9 (18%)	9 (18%)
Necrosis				1 (2%)
Glands, cyst		1 (2%)		
Goblet cell, hyperplasia	2 (4%)		1 (2%)	
Nasolacrimal duct, inflammation	1 (2%)	1 (2%)	1 (2%)	
Olfactory epithelium, inflammation				1 (2%)
Olfactory epithelium, metaplasia				1 (2%)
Respiratory epithelium, hyperplasia	9 (18%)	7 (14%)	9 (18%)	6 (12%)
Respiratory epithelium, inflammation	1 (2%)			3 (6%)
Respiratory epithelium, metaplasia, squamous	1 (2%)			1 (2%)
Respiratory epithelium, ulcer	1 (2%)		1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Special Senses System				
Eye	(1)	(1)		
Lens, cataract	1 (100%)			
Retina, degeneration	1 (100%)			
Zymbal's gland	(1)		(1)	(1)
Cyst				1 (100%)
Hyperplasia				1 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		4 (8%)	1 (2%)	10 (20%)
Hemorrhage		1 (2%)		
Infarct	2 (4%)			1 (2%)
Inflammation		1 (2%)		
Mineralization	1 (2%)	1 (2%)	1 (2%)	9 (18%)
Necrosis	1 (2%)			1 (2%)
Nephropathy	47 (94%)	43 (86%)	47 (94%)	48 (96%)
Pigmentation	9 (18%)	6 (12%)	9 (18%)	2 (4%)
Renal tubule, hyperplasia	2 (4%)	2 (4%)	4 (8%)	12 (24%)
Transitional epithelium, hyperplasia	12 (24%)	14 (28%)	15 (30%)	34 (68%)
Urinary bladder	(49)	(49)	(50)	(49)
Hemorrhage	1 (2%)	2 (4%)		1 (2%)
Inflammation	1 (2%)	3 (6%)	1 (2%)	
Necrosis		1 (2%)		
Transitional epithelium, hyperplasia		2 (4%)	1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF ETHYLBENZENE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	14	8	6
Natural deaths	12	5	8	8
Survivors				
Died last week of study	1			
Terminal sacrifice	30	31	34	35
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Intestine large, colon	(47)	(49)	(48)	(49)
Intestine large, rectum	(49)	(50)	(47)	(49)
Polyp adenomatous			1 (2%)	
Intestine large, cecum	(44)	(50)	(47)	(49)
Intestine small, duodenum	(47)	(48)	(47)	(48)
Intestine small, jejunum	(41)	(49)	(47)	(45)
Intestine small, ileum	(41)	(48)	(47)	(46)
Liver	(50)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Mesentery	(7)	(4)	(6)	(7)
Oral mucosa				(1)
Pharyngeal, squamous cell papilloma				1 (100%)
Pancreas	(49)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(49)
Stomach, forestomach	(49)	(50)	(50)	(49)
Stomach, glandular	(49)	(49)	(49)	(49)
Tongue			(1)	(1)
Schwannoma malignant				1 (100%)
Squamous cell papilloma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(49)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adenoma		1 (2%)	1 (2%)	
Carcinoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)	2 (4%)	
Pheochromocytoma benign	2 (4%)			
Bilateral, pheochromocytoma benign		2 (4%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	1 (2%)		1 (2%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Endocrine System (continued)				
Pituitary gland	(49)	(49)	(50)	(49)
Pars distalis, adenoma	27 (55%)	17 (35%)	24 (48%)	24 (49%)
Pars distalis, adenoma, multiple	3 (6%)	6 (12%)	1 (2%)	3 (6%)
Pars distalis, carcinoma		1 (2%)	1 (2%)	
Thyroid gland	(48)	(50)	(50)	(49)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	2 (4%)	3 (6%)	2 (4%)	3 (6%)
C-cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(47)	(49)	(48)	(47)
Adenoma	2 (4%)			
Carcinoma	1 (2%)		1 (2%)	
Ovary	(50)	(50)	(50)	(49)
Histiocytic sarcoma				1 (2%)
Uterus	(50)	(50)	(50)	(49)
Polyp stromal	2 (4%)	3 (6%)	4 (8%)	3 (6%)
Bilateral, polyp stromal			1 (2%)	
Endometrium, sarcoma stromal		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Lymph node	(3)	(3)	(4)	(4)
Lumbar, histiocytic sarcoma	1 (33%)			
Lymph node, bronchial	(37)	(34)	(41)	(38)
Lymph node, mandibular	(49)	(50)	(50)	(49)
Lymph node, mesenteric	(49)	(50)	(50)	(49)
Lymph node, mediastinal	(49)	(49)	(50)	(49)
Rhabdomyosarcoma, metastatic, uncertain primary site			1 (2%)	
Spleen	(49)	(50)	(49)	(49)
Thymus	(48)	(47)	(47)	(47)
Rhabdomyosarcoma, metastatic, uncertain primary site			1 (2%)	
Integumentary System				
Mammary gland	(48)	(50)	(49)	(49)
Adenoma	1 (2%)	2 (4%)		1 (2%)
Carcinoma	2 (4%)	1 (2%)	2 (4%)	
Carcinoma, multiple	1 (2%)			1 (2%)
Fibroadenoma	13 (27%)	18 (36%)	18 (37%)	15 (31%)
Fibroadenoma, multiple	6 (13%)	1 (2%)	3 (6%)	6 (12%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma			2 (4%)	
Sebaceous gland, carcinoma				1 (2%)
Subcutaneous tissue, fibroma	1 (2%)			
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma		1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)		
Musculoskeletal System				
Skeletal muscle		(1)		
Nervous System				
Brain	(50)	(50)	(50)	(49)
Astrocytoma malignant	1 (2%)			
Carcinoma, metastatic, pituitary gland		1 (2%)	1 (2%)	
Respiratory System				
Larynx	(45)	(43)	(44)	(45)
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)	
Alveolar/bronchiolar adenoma, multiple		1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, uncertain primary site		1 (2%)		
Mediastinum, sarcoma, metastatic, uncertain primary site		1 (2%)		
Nose	(50)	(50)	(50)	(49)
Glands, adenoma		1 (2%)		
Trachea	(50)	(50)	(50)	(49)
Special Senses System				
Ear	(3)			
External ear, sarcoma	1 (33%)			
Zymbal's gland	(1)	(1)		
Adenoma	1 (100%)			
Carcinoma		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Renal tubule, adenoma				1 (2%)
Urinary bladder	(48)	(49)	(49)	(48)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(49)
Histiocytic sarcoma	2 (4%)			1 (2%)
Leukemia granulocytic		1 (2%)		
Leukemia mononuclear	13 (26%)	18 (36%)	16 (32%)	11 (22%)
Lymphoma malignant	1 (2%)	1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	45	43	46
Total primary neoplasms	84	84	84	74
Total animals with benign neoplasms	37	39	37	39
Total benign neoplasms	62	57	60	58
Total animals with malignant neoplasms	20	24	21	14
Total malignant neoplasms	22	27	24	16
Total animals with metastatic neoplasms		2	3	
Total metastatic neoplasms		3	4	
Total animals with malignant neoplasms of uncertain primary site		1	1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control

Number of Days on Study	0 1 1 3 4 4 5 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 1 1 9 1 8 9 0 3 5 5 5 6 6 8 8 8 0 2 2 3 3 3 3 3 3 8 1 4 8 6 6 7 8 1 4 9 5 8 3 6 7 4 1 7 4 4 4 4 4 5
Carcass ID Number	0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 9 6 6 0 9 6 5 5 5 8 7 9 8 9 8 7 8 7 8 5 6 6 8 9 5 1 2 9 0 7 5 6 3 8 6 6 3 1 0 4 1 9 0 7 7 0 7 3 6 2
Alimentary System	
Esophagus	+ +
Intestine large, colon	A A A +
Intestine large, rectum	+ + A +
Intestine large, cecum	A A A + + + + + + + + A A + A + + + + + + + + + +
Intestine small, duodenum	A A A +
Intestine small, jejunum	A A A A A + + + + + + A + + A + + A + + + + + + +
Intestine small, ileum	A A A A + + + + + + A A A + A + A + + + + + + + +
Liver	+ +
Histiocytic sarcoma	X
Mesentery	+ + + + + + +
Pancreas	+ A +
Histiocytic sarcoma	X
Salivary glands	+ +
Stomach, forestomach	+ A +
Stomach, glandular	+ A +
Tooth	+
Cardiovascular System	
Blood vessel	+ + + + + M + + + + + + + + + + + + + + + + + + +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma benign	X
Islets, pancreatic	+ +
Adenoma	X
Parathyroid gland	+ + M + + + + + + + + + + + + + + + + + M + + + + +
Pituitary gland	+ + + + + + + + + + + + + + A + + + + + + + + + +
Pars distalis, adenoma	X X X X X X X X
Pars distalis, adenoma, multiple	X X
Thyroid gland	+ A M +
C-cell, adenoma	X X
General Body System	
None	
Genital System	
Clitoral gland	+ + + + + + + + + + + + + + + + M + + + + M + + + +
Adenoma	
Carcinoma	
Ovary	+ +
Uterus	+ +
Polyp stromal	X

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 5 4	0 5 5	0 5 9	0 6 1	0 6 3	0 6 4	0 7 3	0 7 4	0 7 7	0 7 9	0 8 5	0 9 2	0 9 5	0 5 1	0 6 6	0 6 8	0 7 2	0 7 5	0 7 8	0 8 0	0 8 2	0 8 8	0 9 4	0 9 8	0 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery																							+			7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X																		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X	X			X			X			X	X		X		X	X	X	X	X	X	X	X	27
Pars distalis, adenoma, multiple											X															3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma		X					X																			2
Carcinoma					X																					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X																									2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	0 1 8	1 1 1	1 9 4	3 1 8	4 8 6	4 9 6	5 0 7	6 3 8	6 5 1	6 5 4	6 5 9	6 6 5	6 6 8	6 8 3	6 8 6	6 8 7	7 0 4	7 2 1	7 2 7	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5
Carcass ID Number	0 9 1	0 6 2	0 6 9	1 0 0	0 9 7	0 6 5	0 5 6	0 5 3	0 5 8	0 8 6	0 7 6	0 9 3	0 8 1	0 9 0	0 8 4	0 7 1	0 8 9	0 7 0	0 8 7	0 5 7	0 6 0	0 6 7	0 8 3	0 9 6	0 5 2
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+														+							
Lumbar, histiocytic sarcoma																		X							
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Carcinoma																	X								
Carcinoma, multiple																				X					
Fibroadenoma																X		X		X			X		X
Fibroadenoma, multiple																			X		X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant						X																			
Respiratory System																									
Larynx	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Histiocytic sarcoma														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear														+											
External ear, sarcoma														X											
Eye																									
Zymbal's gland																							+		
Adenoma																							X		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X				X							
Leukemia mononuclear							X		X	X		X					X		X						
Lymphoma malignant				X																					

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 5 4	0 5 5	0 5 9	0 6 1	0 6 3	0 6 4	0 7 3	0 7 4	0 7 7	0 7 9	0 8 5	0 9 2	0 9 5	0 5 1	0 6 6	0 6 8	0 7 2	0 7 5	0 7 8	0 8 0	0 8 2	0 8 8	0 9 4	0 9 8	0 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node		+																								3
Lumbar, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	+	M	M	M	+	+	+	+	+	M	M	+	+	M	+	+	+	M	+	M	+	+	37
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Carcinoma			X																							2
Carcinoma, multiple																										1
Fibroadenoma				X					X		X					X			X	X		X		X		13
Fibroadenoma, multiple						X	X														X		X			6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																	+	+								3
External ear, sarcoma																										1
Eye																+										1
Zymbal's gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Leukemia mononuclear		X		X		X		X								X			X		X				13
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm

Number of Days on Study	4 1 2	4 6 2	4 7 5	5 0 6	5 3 1	6 0 1	6 0 9	6 0 9	6 1 0	6 3 6	6 4 6	6 4 7	6 6 8	6 8 6	7 1 9	7 2 4	7 2 4	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 4 4	7 4 5	7 4 5
Carcass ID Number	1 7 4	1 5 2	1 5 9	1 7 5	1 8 6	1 6 8	1 8 8	1 9 9	1 7 3	1 8 5	1 5 8	1 8 2	1 7 7	1 6 6	1 7 9	1 9 2	1 9 5	1 5 5	1 9 1	1 6 3	1 6 4	1 8 3	1 9 8	1 5 6	1 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Bilateral, pheochromocytoma benign															X		X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X			X					X			X				X			X	X	
Pars distalis, adenoma, multiple																			X						
Pars distalis, carcinoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																			X						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X						X					X								
Endometrium, sarcoma stromal		X																							
Vagina					+	+											+								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+		+				+							
Lymph node, bronchial	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	M	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	16909	17000	17101	17808	18000	18404	18707	19303	19606	19907	15111	15313	15414	15707	16000	16101	16505	16707	17202	17606	18101	18909	19004	19404	20006	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																				+		+			+	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant										X																1
Bilateral, pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X							X				X		X	X			X	X		X		X			17
Pars distalis, adenoma, multiple				X			X		X											X		X				6
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																				X						1
C-cell, adenoma										X														X		3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										3
Endometrium, sarcoma stromal																										1
Vagina																										3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Lymph node, bronchial	M	M	+	+	M	M	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	34
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	4 1 2	4 6 2	4 7 5	5 0 6	5 3 1	6 0 1	6 0 9	6 0 9	6 1 0	6 3 6	6 4 6	6 4 7	6 6 8	6 8 6	7 1 9	7 2 4	7 2 4	7 3 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5
Carcass ID Number	1 7 4	1 5 2	1 5 9	1 7 5	1 8 6	1 6 8	1 8 8	1 9 9	1 7 3	1 8 5	1 5 8	1 8 2	1 7 7	1 6 6	1 7 9	1 9 2	1 9 5	1 5 5	1 9 1	1 6 3	1 6 4	1 8 3	1 9 8	1 5 6	1 6 2
Hematopoietic System (continued)																									
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Fibroadenoma												X	X			X	X	X	X		X	X			X
Fibroadenoma, multiple							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																				X					
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland															X										
Respiratory System																									
Larynx	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple																									
Sarcoma, metastatic, uncertain primary site						X																			
Mediastinum, sarcoma, metastatic, uncertain primary site						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glands, adenoma													X												
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland								+																	
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic				X																					
Leukemia mononuclear	X									X	X	X		X	X			X					X		X
Lymphoma malignant									X																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	16969	17070	17171	17878	18080	18484	18787	19393	19696	19797	15111	15313	15424	15757	16020	16161	16565	16667	16772	17626	17681	18189	18990	19004	20020	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																	X								2
Carcinoma																		X								1
Fibroadenoma	X						X		X				X			X						X	X	X	X	18
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma																				X						1
Subcutaneous tissue, sarcoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	43
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple					X																					1
Sarcoma, metastatic, uncertain primary site																										1
Mediastinum, sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glands, adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Leukemia mononuclear					X		X		X			X	X					X	X					X	X	18
Lymphoma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm

Number of Days on Study	3 9 3	4 4 9	4 8 6	5 0 2	6 0 2	6 2 4	6 5 1	6 5 8	6 5 9	6 6 2	6 7 4	6 8 5	6 8 9	6 9 4	6 9 9	7 0 9	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 5 6	2 7 2	3 0 0	2 6 5	2 8 6	2 9 7	2 6 9	2 9 5	2 5 8	2 7 4	2 8 4	2 8 7	2 5 7	2 6 6	2 7 8	2 8 3	2 6 2	2 7 1	2 5 1	2 5 4	2 5 5	2 6 1	2 6 3	2 6 4	2 6 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																							X		
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+						+	+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant									X					X											
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X					X		X				X	X					X	X	X	X
Pars distalis, adenoma, multiple																			X						
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Bilateral, polyp stromal																		X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	27 3	27 6	27 7	27 9	28 1	28 2	28 9	29 0	29 2	29 3	29 4	25 2	25 3	25 9	26 0	26 8	27 0	27 5	28 0	28 5	28 8	29 1	29 6	29 8	29 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery													+			+	+									6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue												+														1
Squamous cell papilloma												X														1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Carcinoma																									X	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
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		24
Pars distalis, adenoma, multiple																										1
Pars distalis, carcinoma																		X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																									X	2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X		X								X		X							4
Bilateral, polyp stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	3 9 3	4 4 9	4 8 6	5 0 2	6 0 2	6 2 4	6 5 1	6 5 8	6 5 9	6 6 2	6 7 4	6 8 5	6 8 9	6 9 4	6 9 9	7 0 9	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	2 5 6	2 7 2	3 0 0	2 6 5	2 8 6	2 9 7	2 6 9	2 9 5	2 5 8	2 7 4	2 8 4	2 8 7	2 5 7	2 6 6	2 7 8	2 8 3	2 6 2	2 7 1	2 5 1	2 5 4	2 5 5	2 6 1	2 6 3	2 6 4	2 6 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+				+	+		+												
Lymph node, bronchial	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, uncertain primary site	X																								
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, uncertain primary site	X																								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X						X															
Fibroadenoma							X					X		X	X				X	X			X		
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																	X								
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Respiratory System																									
Larynx	M	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, mammary gland				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																			+				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X				X	X		X	X	X					X				X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	27 3	27 6	27 7	27 9	28 1	28 2	28 9	29 0	29 2	29 3	29 4	25 2	25 3	25 9	26 0	26 8	27 0	27 5	28 0	28 5	28 8	29 1	29 6	29 8	29 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										4
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	41
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Rhabdomyosarcoma, metastatic, uncertain primary site																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										2
Fibroadenoma		X	X		X	X	X	X	X							X						X	X		X	18
Fibroadenoma, multiple	X														X			X								3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma														X							X					2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																		X								1
Respiratory System																										
Larynx	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												1
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																				+						3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X				X				X						X						X		X	16

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm

Number of Days on Study	4 4 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	4 6 0 2 4 5 6 9 9 0 0 1 2 2 3 3 3 3 3 3 3 3 3 3
	8 2 4 9 6 5 7 0 9 3 9 1 2 3 4 4 4 4 4 5 5 5 5 5
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	5 5 5 5 7 9 7 7 8 9 6 6 7 5 6 6 8 8 9 5 6 6 7 7
	3 6 8 1 7 6 3 8 8 5 7 3 5 2 8 9 2 7 2 7 1 5 4 6
Alimentary System	
Esophagus	+ +
Intestine large, colon	+ +
Intestine large, rectum	+ +
Intestine large, cecum	+ +
Intestine small, duodenum	A +
Intestine small, jejunum	+ + + A A A + A + + + + + + + + + + + + + + + +
Intestine small, ileum	A A + + A + + + + + + + + + + + + + + + + + + +
Liver	+ +
Mesentery	+ + + +
Oral mucosa	
Pharyngeal, squamous cell papilloma	
Pancreas	+ +
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tongue	+
Schwannoma malignant	X
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
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, adenoma, multiple	X
Thyroid gland	+ +
C-cell, adenoma	X
C-cell, carcinoma	
General Body System	
None	
Genital System	
Clitoral gland	+ + + + + + + + + + M + + + + + + + + + + + + +
Ovary	+ +
Histiocytic sarcoma	
Uterus	+ +
Polyp stromal	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	37909	38101	38404	38505	38606	39000	39303	39404	39707	39909	40454	40554	40559	40600	40602	40604	40606	40700	40720	40800	40803	40889	40901	40980	41040	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery														+			+		+						+	7
Oral mucosa															+											1
Pharyngeal, squamous cell papilloma															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Schwannoma malignant																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X						X	X	X		X	X	X		X	X		X			X	24
Pars distalis, adenoma, multiple			X																					X		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X							X																	3
C-cell, carcinoma																						X				1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal				X												X			X							3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	4 4 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 4 6 0 2 4 5 6 9 9 0 0 1 2 2 3 3 3 3 3 3 3 3 3 8 2 4 9 6 5 7 0 9 3 9 1 2 3 4 4 4 4 4 5 5 5 5 5
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 5 5 5 5 7 9 7 7 8 9 6 6 7 5 6 6 8 8 9 5 6 6 7 7 3 6 8 1 7 6 3 8 8 5 7 3 5 2 8 9 2 7 2 7 1 5 4 6
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, bronchial	+ + M + M + + + + + + M + + + M M M M + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Lymph node, mediastinal	+ +
Spleen	+ +
Thymus	+ +
Integumentary System	
Mammary gland	+ +
Adenoma	X
Carcinoma, multiple	
Fibroadenoma	X X X X X X X
Fibroadenoma, multiple	X X X X
Skin	+ +
Sebaceous gland, carcinoma	
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Larynx	+ + M + + + + + M + + M + + + + + + + + + + +
Lung	+ +
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	
Harderian gland	+
Urinary System	
Kidney	+ +
Renal tubule, adenoma	
Urinary bladder	+ + + + A + + + + + + + + + + + + + + + + + + +
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	
Leukemia mononuclear	X X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	37909	38101	38404	38505	38606	38900	39303	39404	39707	39909	39954	40055	40559	40660	40962	41064	41166	41270	41472	41580	41883	41989	42091	42188	42240	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																		+	+							4
Lymph node, bronchial	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	38
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma, multiple																			X							1
Fibroadenoma		X	X					X	X			X				X				X	X		X			15
Fibroadenoma, multiple													X	X	X											6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sebaceous gland, carcinoma										X																1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye										+																1
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma	X																									1
Leukemia mononuclear									X	X						X		X	X							11

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate[a]	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/49 (0%)
Adjusted rate[b]	6.5%	8.6%	5.0%	0.0%
Terminal rate[c]	2/31 (6%)	1/31 (3%)	0/34 (0%)	0/35 (0%)
First incidence (days)	734 (T)	719	659	—[e]
Life table test[d]	P = 0.101N	P = 0.516	P = 0.664N	P = 0.212N
Logistic regression test[d]	P = 0.105N	P = 0.514	P = 0.678N	P = 0.212N
Cochran-Armitage test[d]	P = 0.120N			
Fisher exact test[d]		P = 0.500	P = 0.691N	P = 0.253N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/47 (6%)	0/49 (0%)	1/48 (2%)	0/47 (0%)
Adjusted rate	10.3%	0.0%	3.1%	0.0%
Terminal rate	3/29 (10%)	0/30 (0%)	1/32 (3%)	0/34 (0%)
First incidence (days)	734 (T)	—	734 (T)	—
Life table test	P = 0.137N	P = 0.114N	P = 0.269N	P = 0.094N
Logistic regression test	P = 0.137N	P = 0.114N	P = 0.268N	P = 0.094N
Cochran-Armitage test	P = 0.162N			
Fisher exact test		P = 0.113N	P = 0.301N	P = 0.121N
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	7/49 (14%)
Adjusted rate	0.0%	0.0%	2.9%	19.4%
Terminal rate	0/31 (0%)	0/31 (0%)	1/34 (3%)	6/35 (17%)
First incidence (days)	—	—	734 (T)	722
Life table test	P < 0.001	—[f]	P = 0.518	P = 0.015
Logistic regression test	P < 0.001	—	P = 0.518	P = 0.014
Cochran-Armitage test	P < 0.001			
Fisher exact test		—	P = 0.500	P = 0.006
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	8/49 (16%)
Adjusted rate	0.0%	0.0%	2.9%	22.2%
Terminal rate	0/31 (0%)	0/31 (0%)	1/34 (3%)	7/35 (20%)
First incidence (days)	—	—	734 (T)	722
Life table test	P < 0.001	—	P = 0.518	P = 0.008
Logistic regression test	P < 0.001	—	P = 0.518	P = 0.007
Cochran-Armitage test	P < 0.001			
Fisher exact test		—	P = 0.500	P = 0.003
Mammary Gland: Fibroadenoma				
Overall rate	19/50 (38%)	19/50 (38%)	21/50 (42%)	21/49 (43%)
Adjusted rate	55.8%	49.7%	55.0%	53.8%
Terminal rate	16/31 (52%)	12/31 (39%)	17/34 (50%)	17/35 (49%)
First incidence (days)	687	609	651	699
Life table test	P = 0.512N	P = 0.564N	P = 0.561	P = 0.541N
Logistic regression test	P = 0.549N	P = 0.554N	P = 0.509	P = 0.543N
Cochran-Armitage test	P = 0.333			
Fisher exact test		P = 0.582N	P = 0.419	P = 0.387

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	20/50 (40%)	20/50 (40%)	21/50 (42%)	21/49 (43%)
Adjusted rate	56.9%	52.3%	55.0%	53.8%
Terminal rate	16/31 (52%)	13/31 (42%)	17/34 (50%)	17/35 (49%)
First incidence (days)	651	609	651	699
Life table test	P = 0.421N	P = 0.567N	P = 0.519N	P = 0.458N
Logistic regression test	P = 0.454N	P = 0.550N	P = 0.575N	P = 0.466N
Cochran-Armitage test	P = 0.419			
Fisher exact test		P = 0.581N	P = 0.500	P = 0.466
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/49 (2%)
Adjusted rate	9.2%	3.2%	4.5%	2.9%
Terminal rate	2/31 (6%)	1/31 (3%)	0/34 (0%)	1/35 (3%)
First incidence (days)	704	734 (T)	502	734 (T)
Life table test	P = 0.306N	P = 0.301N	P = 0.471N	P = 0.263N
Logistic regression test	P = 0.353N	P = 0.295N	P = 0.511N	P = 0.266N
Cochran-Armitage test	P = 0.351N			
Fisher exact test		P = 0.309N	P = 0.500N	P = 0.316N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	2/49 (4%)
Adjusted rate	11.4%	6.5%	4.5%	5.7%
Terminal rate	2/31 (6%)	2/31 (6%)	0/34 (0%)	2/35 (6%)
First incidence (days)	651	734 (T)	502	734 (T)
Life table test	P = 0.327N	P = 0.342N	P = 0.313N	P = 0.290N
Logistic regression test	P = 0.378N	P = 0.322N	P = 0.349N	P = 0.303N
Cochran-Armitage test	P = 0.385N			
Fisher exact test		P = 0.339N	P = 0.339N	P = 0.349N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	22/50 (44%)	20/50 (40%)	23/50 (46%)	22/49 (45%)
Adjusted rate	61.0%	52.3%	57.0%	56.3%
Terminal rate	17/31 (55%)	13/31 (42%)	17/34 (50%)	18/35 (51%)
First incidence (days)	651	609	502	699
Life table test	P = 0.396N	P = 0.412N	P = 0.509N	P = 0.367N
Logistic regression test	P = 0.449N	P = 0.377N	P = 0.561N	P = 0.368N
Cochran-Armitage test	P = 0.436			
Fisher exact test		P = 0.420N	P = 0.500	P = 0.545
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	30/49 (61%)	23/49 (47%)	25/50 (50%)	27/49 (55%)
Adjusted rate	78.5%	61.2%	63.6%	65.4%
Terminal rate	23/31 (74%)	17/31 (55%)	20/34 (59%)	21/35 (60%)
First incidence (days)	496	475	449	629
Life table test	P = 0.298N	P = 0.122N	P = 0.112N	P = 0.155N
Logistic regression test	P = 0.377N	P = 0.061N	P = 0.096N	P = 0.151N
Cochran-Armitage test	P = 0.546			
Fisher exact test		P = 0.112N	P = 0.178N	P = 0.341N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	30/49 (61%)	24/49 (49%)	26/50 (52%)	27/49 (55%)
Adjusted rate	78.5%	62.3%	66.2%	65.4%
Terminal rate	23/31 (74%)	17/31 (55%)	21/34 (62%)	21/35 (60%)
First incidence (days)	496	475	449	629
Life table test	P = 0.264N	P = 0.167N	P = 0.149N	P = 0.155N
Logistic regression test	P = 0.332N	P = 0.089N	P = 0.134N	P = 0.151N
Cochran-Armitage test	P = 0.511N			
Fisher exact test		P = 0.155N	P = 0.235N	P = 0.341N
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted rate	0.0%	0.0%	8.8%	0.0%
Terminal rate	0/31 (0%)	0/31 (0%)	3/34 (9%)	0/35 (0%)
First incidence (days)	—	—	734 (T)	—
Life table test	P = 0.617N	—	P = 0.137	—
Logistic regression test	P = 0.617N	—	P = 0.137	—
Cochran-Armitage test	P = 0.656N			
Fisher exact test		—	P = 0.121	—
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/48 (4%)	4/50 (8%)	2/50 (4%)	3/49 (6%)
Adjusted rate	6.2%	12.4%	5.9%	8.6%
Terminal rate	1/31 (3%)	3/31 (10%)	2/34 (6%)	3/35 (9%)
First incidence (days)	721	731	734 (T)	734 (T)
Life table test	P = 0.580N	P = 0.348	P = 0.666N	P = 0.554
Logistic regression test	P = 0.585N	P = 0.354	P = 0.675N	P = 0.558
Cochran-Armitage test	P = 0.567			
Fisher exact test		P = 0.359	P = 0.676N	P = 0.510
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/48 (4%)	4/50 (8%)	2/50 (4%)	4/49 (8%)
Adjusted rate	6.2%	12.4%	5.9%	11.4%
Terminal rate	1/31 (3%)	3/31 (10%)	2/34 (6%)	4/35 (11%)
First incidence (days)	721	731	734 (T)	734 (T)
Life table test	P = 0.436	P = 0.348	P = 0.666N	P = 0.394
Logistic regression test	P = 0.431	P = 0.354	P = 0.675N	P = 0.396
Cochran-Armitage test	P = 0.371			
Fisher exact test		P = 0.359	P = 0.676N	P = 0.349
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	3/49 (6%)
Adjusted rate	6.2%	7.5%	14.7%	8.6%
Terminal rate	1/31 (3%)	0/31 (0%)	5/34 (15%)	3/35 (9%)
First incidence (days)	721	601	734 (T)	734 (T)
Life table test	P = 0.569	P = 0.511	P = 0.252	P = 0.554
Logistic regression test	P = 0.546	P = 0.508	P = 0.238	P = 0.558
Cochran-Armitage test	P = 0.495			
Fisher exact test		P = 0.500	P = 0.218	P = 0.490

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	5/50 (10%)	3/49 (6%)
Adjusted rate	6.2%	9.3%	14.7%	8.6%
Terminal rate	1/31 (3%)	0/31 (0%)	5/34 (15%)	3/35 (9%)
First incidence (days)	721	462	734 (T)	734 (T)
Life table test	P = 0.545N	P = 0.355	P = 0.252	P = 0.554
Logistic regression test	P = 0.585	P = 0.309	P = 0.238	P = 0.558
Cochran-Armitage test	P = 0.568			
Fisher exact test		P = 0.339	P = 0.218	P = 0.490
All Organs: Mononuclear Cell Leukemia				
Overall rate	13/50 (26%)	18/50 (36%)	16/50 (32%)	11/49 (22%)
Adjusted rate	34.0%	46.2%	38.3%	25.0%
Terminal rate	7/31 (23%)	11/31 (35%)	9/34 (26%)	5/35 (14%)
First incidence (days)	507	412	486	448
Life table test	P = 0.118N	P = 0.217	P = 0.429	P = 0.315N
Logistic regression test	P = 0.195N	P = 0.222	P = 0.370	P = 0.458N
Cochran-Armitage test	P = 0.196N			
Fisher exact test		P = 0.194	P = 0.330	P = 0.430N
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	39/50 (78%)	37/50 (74%)	39/49 (80%)
Adjusted rate	90.1%	88.5%	88.0%	86.7%
Terminal rate	27/31 (87%)	26/31 (84%)	29/34 (85%)	29/35 (83%)
First incidence (days)	496	475	449	629
Life table test	P = 0.293N	P = 0.441	P = 0.341N	P = 0.386N
Logistic regression test	P = 0.444N	P = 0.565	P = 0.381N	P = 0.500N
Cochran-Armitage test	P = 0.346			
Fisher exact test		P = 0.408	P = 0.590N	P = 0.337
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	25/50 (50%)	22/50 (44%)	14/49 (29%)
Adjusted rate	47.8%	56.7%	49.2%	31.9%
Terminal rate	10/31 (32%)	13/31 (42%)	12/34 (35%)	7/35 (20%)
First incidence (days)	318	412	393	448
Life table test	P = 0.029N	P = 0.264	P = 0.538	P = 0.107N
Logistic regression test	P = 0.055N	P = 0.335	P = 0.527	P = 0.165N
Cochran-Armitage test	P = 0.044N			
Fisher exact test		P = 0.211	P = 0.420	P = 0.162N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	45/50 (90%)	44/50 (88%)	46/49 (94%)
Adjusted rate	93.3%	90.0%	89.8%	93.9%
Terminal rate	28/31 (90%)	26/31 (84%)	29/34 (85%)	32/35 (91%)
First incidence (days)	318	412	393	448
Life table test	P = 0.389N	P = 0.395	P = 0.470N	P = 0.494N
Logistic regression test	P = 0.236	P = 0.442	P = 0.595	P = 0.318
Cochran-Armitage test	P = 0.124			
Fisher exact test		P = 0.277	P = 0.387	P = 0.106

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, kidney, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposure group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	14	8	6
Natural deaths	12	5	8	8
Survivors				
Died last week of study	1			
Terminal sacrifice	30	31	34	35
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Intestine large, colon	(47)	(49)	(48)	(49)
Inflammation	1 (2%)			
Intestine large, rectum	(49)	(50)	(47)	(49)
Arteriole, inflammation	1 (2%)			
Intestine large, cecum	(44)	(50)	(47)	(49)
Inflammation	1 (2%)			
Intestine small, ileum	(41)	(48)	(47)	(46)
Hyperplasia			1 (2%)	
Inflammation			1 (2%)	
Liver	(50)	(50)	(50)	(49)
Angiectasis	3 (6%)			6 (12%)
Basophilic focus	23 (46%)	29 (58%)	33 (66%)	29 (59%)
Clear cell focus	3 (6%)	3 (6%)	1 (2%)	4 (8%)
Congestion	1 (2%)		1 (2%)	1 (2%)
Degeneration		1 (2%)	2 (4%)	
Eosinophilic focus	2 (4%)	3 (6%)	8 (16%)	5 (10%)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	4 (8%)	4 (8%)	4 (8%)	5 (10%)
Infiltration cellular, lymphocyte			1 (2%)	
Inflammation, acute				1 (2%)
Inflammation, chronic	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Mixed cell focus	5 (10%)		1 (2%)	
Necrosis	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Vacuolization cytoplasmic	11 (22%)	12 (24%)	14 (28%)	14 (29%)
Centrilobular, degeneration	1 (2%)			
Portal vein, thrombosis		1 (2%)		
Mesentery	(7)	(4)	(6)	(7)
Artery, degeneration			1 (17%)	
Artery, inflammation	1 (14%)		1 (17%)	
Fat, necrosis	6 (86%)	4 (100%)	5 (83%)	7 (100%)
Pancreas	(49)	(50)	(50)	(49)
Cyst			1 (2%)	
Inflammation	2 (4%)			
Acinus, atrophy	18 (37%)	18 (36%)	18 (36%)	19 (39%)
Arteriole, inflammation			1 (2%)	1 (2%)
Artery, inflammation	1 (2%)		1 (2%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(49)
Hemorrhage				1 (2%)
Hyperkeratosis	2 (4%)		1 (2%)	
Hyperplasia	3 (6%)	1 (2%)	3 (6%)	8 (16%)
Inflammation	1 (2%)	1 (2%)		6 (12%)
Ulcer	3 (6%)	4 (8%)	1 (2%)	
Stomach, glandular	(49)	(49)	(49)	(49)
Cyst				1 (2%)
Hyperplasia	1 (2%)			
Inflammation				2 (4%)
Necrosis	5 (10%)		1 (2%)	1 (2%)
Pigmentation	1 (2%)			
Ulcer		4 (8%)		1 (2%)
Glands, cyst				1 (2%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(49)
Degeneration			1 (2%)	
Inflammation			1 (2%)	
Aorta, inflammation	1 (2%)			
Heart	(50)	(50)	(50)	(49)
Cardiomyopathy	6 (12%)	1 (2%)		6 (12%)
Fibrosis				1 (2%)
Inflammation			1 (2%)	
Atrium, inflammation			1 (2%)	
Atrium, thrombosis				1 (2%)
Endocardium, hyperplasia		1 (2%)	1 (2%)	
Myocardium, hypertrophy		1 (2%)		
Valve, degeneration	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Angiectasis	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Cytoplasmic alteration	1 (2%)	3 (6%)	1 (2%)	
Degeneration				1 (2%)
Degeneration, cystic	5 (10%)	3 (6%)	2 (4%)	4 (8%)
Hemorrhage	4 (8%)	5 (10%)	2 (4%)	1 (2%)
Hyperplasia	3 (6%)	4 (8%)	2 (4%)	3 (6%)
Hypertrophy			3 (6%)	
Necrosis	1 (2%)		1 (2%)	1 (2%)
Pigmentation			1 (2%)	1 (2%)
Vacuolization cytoplasmic	12 (24%)	5 (10%)	12 (24%)	6 (12%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Hyperplasia	4 (8%)		2 (4%)	2 (4%)
Infiltration cellular, lymphocyte			1 (2%)	
Necrosis		1 (2%)		
Parathyroid gland	(48)	(46)	(42)	(47)
Atrophy	1 (2%)			
Hyperplasia	5 (10%)	2 (4%)	4 (10%)	5 (11%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Endocrine System (continued)				
Pituitary gland	(49)	(49)	(50)	(49)
Cyst	1 (2%)			
Infiltration cellular, mixed cell	1 (2%)			
Necrosis	1 (2%)			
Pars distalis, angiectasis	2 (4%)	16 (33%)	6 (12%)	2 (4%)
Pars distalis, cyst	5 (10%)	1 (2%)	3 (6%)	3 (6%)
Pars distalis, degeneration		1 (2%)		
Pars distalis, hemorrhage		2 (4%)		
Pars distalis, hyperplasia	11 (22%)	9 (18%)	14 (28%)	17 (35%)
Pars distalis, pigmentation		2 (4%)		
Pars intermedia, angiectasis		2 (4%)		
Thyroid gland	(48)	(50)	(50)	(49)
Hyperplasia			1 (2%)	
Inflammation	1 (2%)			
Bilateral, C-cell, hyperplasia				1 (2%)
C-cell, hyperplasia	5 (10%)	5 (10%)	5 (10%)	5 (10%)
C-cell, inflammation	1 (2%)			
Follicle, cyst			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(47)	(49)	(48)	(47)
Cyst				1 (2%)
Hyperplasia	4 (9%)	3 (6%)	1 (2%)	3 (6%)
Inflammation	6 (13%)	5 (10%)	4 (8%)	4 (9%)
Bilateral, hyperplasia				1 (2%)
Ovary	(50)	(50)	(50)	(49)
Cyst	5 (10%)	6 (12%)	5 (10%)	5 (10%)
Corpus luteum, hyperplasia	1 (2%)			
Uterus	(50)	(50)	(50)	(49)
Angiectasis	1 (2%)			
Hydrometra	1 (2%)	3 (6%)	1 (2%)	4 (8%)
Inflammation			1 (2%)	1 (2%)
Endometrium, cyst				1 (2%)
Vagina		(3)		
Fibrosis		1 (33%)		
Arteriole, degeneration		1 (33%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Atrophy	1 (2%)			1 (2%)
Hemorrhage	3 (6%)	2 (4%)		1 (2%)
Hyperplasia	7 (14%)	8 (16%)	7 (14%)	8 (16%)
Hyperplasia, mast cell		1 (2%)		
Myelofibrosis	1 (2%)			
Myelostromal proliferation		1 (2%)	1 (2%)	
Erythroid cell, hyperplasia				1 (2%)
Myeloid cell, hyperplasia		1 (2%)	1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System (continued)				
Lymph node	(3)	(3)	(4)	(4)
Pancreatic, hemorrhage			1 (25%)	1 (25%)
Pancreatic, infiltration cellular, histiocyte				1 (25%)
Renal, hemorrhage				2 (50%)
Renal, pigmentation				1 (25%)
Lymph node, bronchial	(37)	(34)	(41)	(38)
Atrophy	1 (3%)			
Ectasia			1 (2%)	
Hemorrhage	4 (11%)	6 (18%)	5 (12%)	3 (8%)
Hyperplasia, lymphoid		1 (3%)		
Infiltration cellular, histiocyte			1 (2%)	
Necrosis			1 (2%)	
Pigmentation	6 (16%)	7 (21%)	7 (17%)	5 (13%)
Lymph node, mandibular	(49)	(50)	(50)	(49)
Ectasia		1 (2%)	1 (2%)	
Hemorrhage	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, plasma cell	2 (4%)	9 (18%)	4 (8%)	3 (6%)
Infiltration cellular, histiocyte	1 (2%)			
Pigmentation				1 (2%)
Lymph node, mesenteric	(49)	(50)	(50)	(49)
Amyloid deposition	1 (2%)			
Atrophy	1 (2%)			
Ectasia			3 (6%)	
Hemorrhage	8 (16%)	6 (12%)	8 (16%)	7 (14%)
Hyperplasia				1 (2%)
Hyperplasia, plasma cell			1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			
Inflammation	1 (2%)		1 (2%)	
Lymph node, mediastinal	(49)	(49)	(50)	(49)
Edema		1 (2%)		
Hemorrhage	21 (43%)	15 (31%)	13 (26%)	21 (43%)
Hyperplasia, plasma cell	1 (2%)			
Infiltration cellular, histiocyte	1 (2%)			
Necrosis	1 (2%)			
Pigmentation	22 (45%)	22 (45%)	25 (50%)	27 (55%)
Spleen	(49)	(50)	(49)	(49)
Hematopoietic cell proliferation	6 (12%)	3 (6%)	3 (6%)	3 (6%)
Hemorrhage		2 (4%)		
Hyperplasia, lymphoid		1 (2%)		
Necrosis				1 (2%)
Pigmentation	1 (2%)	1 (2%)		
Red pulp, atrophy	1 (2%)			
Thymus	(48)	(47)	(47)	(47)
Atrophy	1 (2%)			
Cyst				2 (4%)
Integumentary System				
Mammary gland	(48)	(50)	(49)	(49)
Galactocele	10 (21%)	10 (20%)	10 (20%)	11 (22%)
Hyperplasia	13 (27%)	19 (38%)	21 (43%)	18 (37%)
Infiltration cellular, lymphocyte		1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(49)
Cyst epithelial inclusion			1 (2%)	
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation, chronic	1 (2%)			
Ulcer	1 (2%)		1 (2%)	2 (4%)
Epidermis, hyperplasia			2 (4%)	1 (2%)
Subcutaneous tissue, fibrosis		1 (2%)		
Subcutaneous tissue, inflammation			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(49)
Fibrous osteodystrophy		1 (2%)		
Hyperostosis	2 (4%)	5 (10%)	5 (10%)	1 (2%)
Turbinate, hyperostosis		2 (4%)	2 (4%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			1 (2%)
Hydrocephalus		1 (2%)		1 (2%)
Necrosis	1 (2%)			
Respiratory System				
Larynx	(45)	(43)	(44)	(45)
Infiltration cellular, lymphocyte		3 (7%)	1 (2%)	
Inflammation		2 (5%)	1 (2%)	2 (4%)
Metaplasia, squamous	1 (2%)			
Respiratory epithelium, hyperplasia			1 (2%)	2 (4%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)		2 (4%)
Lung	(50)	(50)	(50)	(49)
Congestion	5 (10%)		1 (2%)	
Edema		1 (2%)	1 (2%)	
Fibrosis	1 (2%)	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)	2 (4%)	2 (4%)	
Infiltration cellular, histiocyte	2 (4%)	3 (6%)	1 (2%)	3 (6%)
Inflammation, chronic	2 (4%)			3 (6%)
Inflammation, chronic active			1 (2%)	
Inflammation, granulomatous	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia	1 (2%)	5 (10%)	2 (4%)	5 (10%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(49)
Angiectasis			1 (2%)	
Congestion	1 (2%)			
Foreign body	4 (8%)	1 (2%)		1 (2%)
Infiltration cellular, lymphocyte				1 (2%)
Inflammation	10 (20%)	10 (20%)	5 (10%)	1 (2%)
Necrosis			1 (2%)	
Thrombosis	1 (2%)			
Glands, cyst			1 (2%)	
Glands, hyperplasia		1 (2%)	2 (4%)	1 (2%)
Goblet cell, hyperplasia				1 (2%)
Nasolacrimal duct, inflammation	2 (4%)	1 (2%)		
Nasolacrimal duct, metaplasia, squamous	1 (2%)			
Respiratory epithelium, hyperplasia	6 (12%)	7 (14%)	5 (10%)	
Respiratory epithelium, metaplasia, squamous		1 (2%)		
Respiratory epithelium, ulcer		2 (4%)		
Trachea	(50)	(50)	(50)	(49)
Special Senses System				
Eye	(1)		(3)	(1)
Lens, cataract	1 (100%)		2 (67%)	1 (100%)
Retina, degeneration	1 (100%)			1 (100%)
Harderian gland				(1)
Inflammation				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)		4 (8%)
Infarct	1 (2%)		1 (2%)	
Mineralization	8 (16%)	11 (22%)	7 (14%)	
Necrosis			1 (2%)	
Nephropathy	38 (76%)	42 (84%)	43 (86%)	46 (94%)
Pigmentation	4 (8%)	10 (20%)	8 (16%)	3 (6%)
Arteriole, inflammation	1 (2%)			
Renal tubule, degeneration			1 (2%)	
Renal tubule, hyperplasia		1 (2%)	3 (6%)	3 (6%)
Transitional epithelium, hyperplasia				2 (4%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF ETHYLBENZENE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1			1
Moribund	6	2	5	6
Natural deaths	15	12	13	13
Survivors				
Died last week of study			1	
Terminal sacrifice	28	36	31	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(42)	(46)	(44)	(43)
Intestine small, jejunum	(44)	(46)	(44)	(43)
Epithelium, carcinoma		1 (2%)		
Intestine small, ileum	(42)	(46)	(44)	(41)
Liver	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Cholangiocarcinoma		1 (2%)		
Fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Hemangioma	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	17 (34%)	8 (16%)	11 (22%)	10 (20%)
Hepatocellular carcinoma, multiple		1 (2%)	2 (4%)	
Hepatocellular adenoma	11 (22%)	12 (24%)	17 (34%)	17 (34%)
Hepatocellular adenoma, multiple	1 (2%)	4 (8%)		1 (2%)
Hepatocholangiocarcinoma	1 (2%)		1 (2%)	1 (2%)
Mesentery	(1)		(1)	
Hepatocellular carcinoma, metastatic, liver	1 (100%)			
Hepatocholangiocarcinoma, metastatic, liver			1 (100%)	
Pancreas	(49)	(50)	(48)	(48)
Acinus, hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Stomach, forestomach	(48)	(50)	(50)	(47)
Fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(48)	(50)	(50)	(47)
Fibrosarcoma	1 (2%)			
Tooth			(1)	(1)
Odontoma				1 (100%)
Cardiovascular System				
Blood vessel	(48)	(48)	(49)	(47)
Aorta, fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Aorta, hepatocellular carcinoma, metastatic, liver	1 (2%)			
Aorta, sarcoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Cardiovascular System (continued)				
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Pericardium, hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(47)	(47)	(48)	(48)
Adenoma	1 (2%)		1 (2%)	
Carcinoma			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Islets, pancreatic	(49)	(50)	(48)	(48)
Adenoma				1 (2%)
Carcinoma				1 (2%)
Pituitary gland	(44)	(45)	(45)	(47)
Pars distalis, carcinoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Follicular cell, adenoma, multiple				1 (2%)
General Body System				
Tissue NOS	(2)	(3)	(1)	(2)
Fibrosarcoma	1 (50%)			
Fat, hepatocholangiocarcinoma, metastatic, liver			1 (100%)	
Thoracic, hepatocholangiocarcinoma, metastatic, liver	1 (50%)			
Thoracic, sarcoma				1 (50%)
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Leiomyoma		1 (2%)		
Seminal vesicle	(49)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Testes	(49)	(50)	(50)	(50)
Interstitial cell, adenoma	1 (2%)		1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(4)	(7)	(11)	(3)
Fibrosarcoma, metastatic, stomach, glandular	1 (25%)			
Pancreatic, carcinoma				1 (33%)
Popliteal, hemangioma			1 (9%)	
Renal, cholangiocarcinoma, metastatic, liver		1 (14%)		
Renal, fibrosarcoma, metastatic, stomach, glandular	1 (25%)			
Renal, hepatocholangiocarcinoma, metastatic, liver			1 (9%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System (continued)				
Lymph node, bronchial	(14)	(24)	(27)	(27)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (4%)
Fibrosarcoma, metastatic, stomach, glandular	1 (7%)			
Hepatocholangiocarcinoma, metastatic, liver			1 (4%)	
Sarcoma				1 (4%)
Lymph node, mandibular	(43)	(45)	(46)	(44)
Sarcoma, metastatic, nose	1 (2%)			
Lymph node, mesenteric	(45)	(46)	(47)	(48)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Lymph node, mediastinal	(24)	(25)	(27)	(25)
Fibrosarcoma, metastatic, stomach, glandular	1 (4%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (4%)			
Sarcoma				1 (4%)
Spleen	(50)	(50)	(49)	(49)
Thymus	(37)	(37)	(39)	(34)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Sarcoma				1 (3%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Fibrosarcoma	1 (2%)			
Hemangioma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Sternum, fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Skeletal muscle	(2)		(2)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (50%)	
Fibrosarcoma, metastatic, stomach, glandular	1 (50%)			
Hepatocellular carcinoma, metastatic, liver	1 (50%)			
Hepatocholangiocarcinoma, metastatic, liver			1 (50%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Respiratory System				
Larynx	(48)	(49)	(46)	(49)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	8 (16%)	9 (18%)	15 (30%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	5 (10%)	3 (6%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	5 (10%)	3 (6%)	5 (10%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		1 (2%)	1 (2%)
Bronchiole, polyp adenomatous		1 (2%)		
Mediastinum, sarcoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Pleura				(1)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (100%)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(2)	(3)	(2)	
Adenoma	1 (50%)	3 (100%)	2 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrosarcoma, metastatic, stomach, glandular	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)		
Renal tubule, adenoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia granulocytic			1 (2%)	1 (2%)
Lymphoma malignant	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	35	34	40	41
Total primary neoplasms	50	49	60	68
Total animals with benign neoplasms	20	25	26	30
Total benign neoplasms	24	33	35	43
Total animals with malignant neoplasms	21	15	21	16
Total malignant neoplasms	26	16	25	25
Total animals with metastatic neoplasms	9	4	6	5
Total metastatic neoplasms	28	7	17	10

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control

Number of Days on Study	0 2 4	0 2 9	2 0 2	2 8 9	4 6 7	5 1 9	5 2 2	5 4 4	5 5 5	5 6 8	5 8 4	5 8 5	5 8 7	6 1 0	6 1 0	6 1 6	6 3 9	6 4 2	6 5 2	6 9 8	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 2 9	0 4 9	0 3 1	0 1 8	0 1 2	0 4 7	0 1 1	0 4 8	0 4 6	0 4 4	0 3 0	0 2 4	0 2 8	0 1 4	0 4 1	0 1 5	0 4 3	0 3 9	0 3 6	0 0 2	0 0 5	0 0 8	0 0 3	0 0 6	0 1 0
Alimentary System																									
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	M	M	A	M	+	M	M	+	+	M	A	M	M	+	+	+	+	A	A	+	+	+
Intestine large, colon	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	A	+	A	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	+	+
Intestine small, jejunum	A	M	+	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+
Intestine small, ileum	A	+	A	A	+	A	+	+	+	+	+	+	+	A	+	+	M	+	A	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, glandular													X												
Hemangioma																									
Hepatocellular carcinoma				X		X			X	X			X	X	X	X	X	X		X		X			X
Hepatocellular adenoma							X								X						X				
Hepatocellular adenoma, multiple																							X		
Hepatocholangiocarcinoma					X																				
Mesentery																		+							
Hepatocellular carcinoma, metastatic, liver																		X							
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, glandular													X												
Stomach, glandular	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
Cardiovascular System																									
Blood vessel	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Aorta, fibrosarcoma, metastatic, stomach, glandular													X												
Aorta, hepatocellular carcinoma, metastatic, liver				X																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, glandular													X												
Pericardium, hepatocholangiocarcinoma, metastatic, liver					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hepatocellular carcinoma, metastatic, liver																		X							
Adrenal medulla	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	M	+	M	M	+	+	+	+	+	+	M	M	M	+	M	M	M	+	+	M
Pituitary gland	+	+	+	+	+	+	M	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 3	0 1 6	0 1 7	0 2 1	0 2 2	0 2 3	0 2 6	0 2 7	0 3 4	0 3 5	0 3 7	0 3 8	0 4 0	0 4 5	0 5 0	0 0 1	0 0 4	0 0 7	0 0 9	0 1 9	0 2 0	0 2 5	0 3 2	0 3 3	0 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	47
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	33
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach, glandular																										1
Hemangioma																	X									1
Hepatocellular carcinoma				X	X	X													X							17
Hepatocellular adenoma		X		X			X		X	X	X			X				X								11
Hepatocellular adenoma, multiple																										1
Hepatocholangiocarcinoma																										1
Mesentery																										1
Hepatocellular carcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, stomach, glandular																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Aorta, fibrosarcoma, metastatic, stomach, glandular																										1
Aorta, hepatocellular carcinoma, metastatic, liver																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach, glandular																										1
Pericardium, hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma										X																1
Hepatocellular carcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	+	+	M	M	+	M	M	M	M	M	+	+	M	+	M	M	M	M	M	M	M	M	+	+	22
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma								X	X												X					3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	0 2 4	0 2 9	2 0 2	2 8 9	4 6 7	5 1 9	5 2 2	5 4 4	5 5 5	5 6 8	5 8 4	5 8 5	5 8 7	6 1 0	6 1 0	6 1 6	6 3 9	6 4 2	6 5 2	6 9 8	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 2 9	0 4 9	0 3 1	0 1 8	0 1 2	0 4 7	0 1 1	0 4 8	0 4 6	0 4 4	0 3 0	0 2 4	0 2 8	0 1 4	0 4 1	0 1 5	0 4 3	0 3 9	0 3 6	0 0 2	0 0 5	0 0 8	0 0 3	0 1 6	0 1 0
General Body System																									
Tissue NOS					+								+												
Fibrosarcoma													X												
Thoracic, hepatocholangiocarcinoma, metastatic, liver					X																				
Genital System																									
Epididymis	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+					+	+												
Fibrosarcoma, metastatic, stomach, glandular													X												
Renal, fibrosarcoma, metastatic, stomach, glandular													X												
Lymph node, bronchial	M	+	+	M	M	+	+	M	M	M	M	M	+	M	M	M	+	M	M	M	+	+	M	+	M
Fibrosarcoma, metastatic, stomach, glandular													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	+	+	+	+
Sarcoma, metastatic, nose								X																	
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Lymph node, mediastinal	+	+	M	+	+	M	M	M	M	M	+	M	+	+	M	+	M	+	M	M	+	+	M	M	M
Fibrosarcoma, metastatic, stomach, glandular													X												
Hepatocholangiocarcinoma, metastatic, liver					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	M	+	+	M	+	+	M	+	M	M	+	M	+	M	M	M	+	+	+
Hepatocholangiocarcinoma, metastatic, liver					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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sternum, fibrosarcoma, metastatic, stomach, glandular													X												
Skeletal muscle													+					+							
Fibrosarcoma, metastatic, stomach, glandular													X												
Hepatocellular carcinoma, metastatic, liver																		X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 3	0 1 6	0 1 7	0 2 1	0 2 2	0 2 3	0 2 6	0 2 7	0 3 4	0 3 5	0 3 7	0 3 8	0 4 0	0 4 5	0 5 0	0 0 1	0 0 4	0 0 7	0 0 9	0 1 9	0 2 0	0 2 5	0 3 2	0 3 3	0 4 2	Total Tissues/ Tumors
General Body System																										
Tissue NOS																										2
Fibrosarcoma																										1
Thoracic, hepatocholangiocarcinoma, metastatic, liver																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis					+																					1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										4
Fibrosarcoma, metastatic, stomach, glandular																										1
Renal, fibrosarcoma, metastatic, stomach, glandular																										1
Lymph node, bronchial	+	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	14
Fibrosarcoma, metastatic, stomach, glandular																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	43
Sarcoma, metastatic, nose																										1
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mediastinal	M	M	+	M	+	M	M	+	M	+	+	M	+	+	M	+	M	M	+	M	+	M	+	+	+	+	24
Fibrosarcoma, metastatic, stomach, glandular																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	37
Hepatocholangiocarcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sternum, fibrosarcoma, metastatic, stomach, glandular																										1
Skeletal muscle																										2
Fibrosarcoma, metastatic, stomach, glandular																										1
Hepatocellular carcinoma, metastatic, liver																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	0 2 4	0 2 4	2 0 2	2 8 9	4 6 7	5 1 9	5 2 2	5 4 4	5 5 5	5 6 8	5 8 4	5 8 5	5 8 7	6 1 0	6 1 0	6 1 6	6 3 9	6 4 2	6 5 2	6 9 8	7 2 3	7 2 5	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 2 9	0 4 9	0 3 1	0 1 8	0 1 2	0 4 7	0 1 1	0 4 8	0 4 6	0 4 4	0 3 0	0 2 4	0 2 8	0 1 4	0 4 1	0 1 5	0 4 3	0 3 9	0 3 6	0 0 2	0 0 5	0 0 8	0 0 3	0 0 6	1 0
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X	X	X							
Alveolar/bronchiolar carcinoma														X											
Fibrosarcoma, metastatic, stomach, glandular													X												
Hepatocellular carcinoma, metastatic, liver				X		X			X									X		X					
Hepatocholangiocarcinoma, metastatic, liver					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, glandular													X												
Hepatocellular carcinoma, metastatic, liver																X									
Urinary bladder	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X					X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 3	0 1 6	0 1 7	0 2 1	0 2 2	0 2 3	0 2 6	0 2 7	0 3 4	0 3 5	0 3 7	0 3 8	0 4 0	0 4 5	0 5 0	0 0 1	0 0 4	0 0 7	0 0 9	0 1 9	0 2 0	0 2 5	0 3 2	0 3 3	0 4 2	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X	X															5
Alveolar/bronchiolar carcinoma					X																					2
Fibrosarcoma, metastatic, stomach, glandular																										1
Hepatocellular carcinoma, metastatic, liver																										5
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+																+									2
Adenoma	X																									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, stomach, glandular																										1
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm

Number of Days on Study	360	380	485	514	531	536	578	580	594	640	641	677	709	725	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	13	30	29	12	09	20	48	34	19	10	36	01	24	11	02	03	04	06	07	08	15	21	25	27	28
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	M	+	+	A	M	M	+	A	A	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epithelium, carcinoma														X											
Intestine small, ileum	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma												X													
Hemangiosarcoma																									
Hepatoblastoma																									
Hepatocellular carcinoma				X		X		X			X														
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma	X		X						X						X	X					X	X			X
Hepatocellular adenoma, multiple											X							X							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	M	M	M	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma										X															
General Body System																									
Tissue NOS																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																		X							
Penis					+																				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	13 2	13 7	13 8	13 9	14 3	14 4	14 6	14 9	10 5	11 4	11 6	11 7	11 8	12 2	12 3	12 6	13 1	13 3	13 5	14 0	14 1	14 2	14 5	14 7	15 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Epithelium, carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangiosarcoma	X																									1
Hepatoblastoma																				X						1
Hepatocellular carcinoma					X							X									X			X		8
Hepatocellular carcinoma, multiple															X											1
Hepatocellular adenoma							X						X					X		X						12
Hepatocellular adenoma, multiple									X																X	4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	+	+	+	M	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	M	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																									X	2
General Body System																										
Tissue NOS		+				+																			+	3
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Penis																			+							2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	360	380	485	514	531	536	578	580	594	640	641	677	709	725	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	13	30	29	12	09	20	48	34	19	10	36	01	24	11	02	03	04	06	07	08	15	21	25	27	28
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+		+					+		+		+					+				+
Renal, cholangiocarcinoma, metastatic, liver												X													
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	M	M	M	+	+	M	M	M	M	+	+	M	+	+	M	M
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	A	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	M	M	M	M	M	M	M	+	+	+	+	+	+	+	M	M	+	M	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	M	M	M	M	+	M	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X							X	X								X				
Alveolar/bronchiolar adenoma, multiple																				X					
Alveolar/bronchiolar carcinoma															X										
Cholangiocarcinoma, metastatic, liver												X													
Hepatocellular carcinoma, metastatic, liver								X			X														
Bronchiole, polyp adenomatous																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland													+												
Adenoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver												X													
Hepatocellular carcinoma, metastatic, liver											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X																	X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	13272	13377	13388	13399	14043	14044	14046	14049	14055	14144	14166	14177	14188	14222	14233	14266	14311	14333	14355	14400	14411	14422	14455	14477	14505	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										7
Renal, cholangiocarcinoma, metastatic, liver																										1
Lymph node, bronchial	M	M	+	M	M	M	+	+	M	M	M	+	M	M	+	+	M	M	+	M	M	M	+	+	+	24
Lymph node, mandibular	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mediastinal	+	+	+	+	M	+	M	+	M	M	M	M	M	M	M	+	+	+	M	M	M	+	+	M	+	25
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	37
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	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X			X											X						X	8
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																										1
Cholangiocarcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver					X																					3
Bronchiole, polyp adenomatous																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+					+																		3
Adenoma			X					X																		3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm

Number of Days on Study	4 8 0	5 2 4	5 6 3	5 7 0	5 7 4	5 7 9	5 7 9	5 8 8	6 0 2	6 4 2	6 8 0	6 8 3	6 8 8	6 9 1	6 9 6	7 0 5	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 2 2	2 3 0	2 4 5	2 2 4	2 3 5	2 0 3	2 4 1	2 2 5	2 1 4	2 1 8	2 2 8	2 2 1	2 1 5	2 1 9	2 0 1	2 1 0	2 0 5	2 0 9	2 0 2	2 0 4	2 0 7	2 1 1	2 1 2	2 1 6	2 2 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	M	+	A	A	M	M	+	A	A	+	M	+	M	+	+	+	M	+	+	+	+	+	M
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	A	+	A	+	A	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	A	+	+	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	A	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X		X	X	X	X					X	X	X			X									
Hepatocellular carcinoma, multiple								X																	
Hepatocellular adenoma							X							X	X		X		X	X				X	
Hepatocholangiocarcinoma																									
Mesentery																									
Hepatocholangiocarcinoma, metastatic, liver																									
Pancreas	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, hepatocholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																							+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Endocrine System																									
Adrenal cortex	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma															X										
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	M	M	+	M	M	M	+	M	+	M	M	+	M	M	+	M	+	+	M	+	+
Pituitary gland	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS																									
Fat, hepatocholangiocarcinoma, metastatic, liver																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	22303	22306	22307	22309	23101	23102	23303	23404	23606	23707	23808	23909	24303	24707	25006	25308	25513	25717	26040	26242	26444	26646	26848	26949	27050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X			X				11
Hepatocellular carcinoma, multiple											X															2
Hepatocellular adenoma			X	X			X			X				X	X	X	X	X					X			17
Hepatocholangiocarcinoma																		X								1
Mesentery																		+								1
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinus, hepatocholangiocarcinoma, metastatic, liver																		X								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma															X											1
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+	M	+	M	+	M	28
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X														1
General Body System																										
Tissue NOS																		+								1
Fat, hepatocholangiocarcinoma, metastatic, liver																		X								1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma									X																	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	4 8 0	5 2 4	5 6 3	5 7 0	5 7 4	5 7 9	5 7 9	5 8 8	6 0 2	6 4 2	6 8 0	6 8 3	6 8 8	6 9 1	6 9 6	7 0 5	7 2 2	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 2 2	2 3 0	2 4 5	2 2 4	2 3 5	2 0 3	2 4 1	2 2 5	2 1 4	2 1 8	2 2 8	2 2 1	2 1 5	2 1 9	2 0 1	2 1 0	2 0 5	2 0 9	2 0 2	2 0 4	2 0 7	2 1 1	2 1 2	2 1 6	2 2 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+					+		+	+		+		+	+								
Popliteal, hemangioma														X											
Renal, hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, bronchial	M	M	+	M	+	+	M	M	M	M	M	+	+	+	+	+	M	+	M	+	+	M	M	M	+
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Lymph node, mediastinal	M	+	M	+	M	M	M	M	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thymus	+	M	+	M	+	M	+	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Hepatocholangiocarcinoma, metastatic, liver																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X			X	X							
Alveolar/bronchiolar adenoma, multiple									X																
Alveolar/bronchiolar carcinoma								X		X					X					X					
Hepatocellular carcinoma, metastatic, liver					X			X			X		X												
Hepatocholangiocarcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung								X																	
Renal tubule, adenoma																									
Ureter																+		+							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 2 3	2 2 6	2 2 7	2 2 9	2 3 1	2 3 2	2 3 3	2 3 4	2 3 6	2 3 7	2 3 8	2 3 9	2 4 3	2 4 7	2 0 6	2 0 8	2 1 3	2 1 7	2 4 0	2 4 2	2 4 4	2 4 6	2 4 8	2 4 9	2 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+					+												+								11
Popliteal, hemangioma																										1
Renal, hepatocholangiocarcinoma, metastatic, liver																		X								1
Lymph node, bronchial	M	M	M	M	+	+	+	M	+	M	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	27
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Lymph node, mediastinal	+	+	+	M	+	M	+	M	+	+	M	M	+	+	M	+	M	M	M	M	M	+	+	M	+	27
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M	39
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																		+								2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X			X			X						X							X		9
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma										X																5
Hepatocellular carcinoma, metastatic, liver																			X							5
Hepatocholangiocarcinoma, metastatic, liver																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland														+					+							2
Adenoma														X					X							2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Renal tubule, adenoma																		X								1
Ureter																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	8	2	6	7	7	7	7	8	0	4	8	8	8	9	9	0	2	2	2	2	2	2	2	2	2
	0	4	3	0	4	9	9	8	2	2	0	3	8	1	6	5	2	4	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	2	3	4	2	3	0	4	2	1	1	2	2	1	1	0	1	0	0	0	0	0	1	1	1	2
	2	0	5	4	5	3	1	5	4	8	8	1	5	9	1	0	5	9	2	4	7	1	2	6	0
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic		X																							
Lymphoma malignant											X							X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 2 3	2 2 6	2 2 7	2 2 9	2 3 1	2 3 2	2 3 3	2 3 4	2 3 6	2 3 7	2 3 8	2 3 9	2 4 3	2 4 7	2 4 6	2 0 6	2 0 8	2 1 3	2 1 7	2 4 0	2 4 2	2 4 4	2 4 6	2 4 8	2 4 9	2 5 0	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Lymphoma malignant		X																								3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm

Number of Days on Study	1 7 9	2 5 9	4 1 8	4 3 0	4 8 0	5 2 0	5 6 5	5 8 2	6 0 7	6 1 8	6 3 2	6 4 7	6 5 9	6 5 9	6 6 0	6 6 9	6 7 9	6 7 9	7 0 8	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 6	3 1 5	3 3 8	3 2 4	3 3 9	3 2 0	3 0 6	3 0 7	3 3 4	3 0 5	3 2 8	3 4 6	3 0 1	3 4 7	3 3 7	3 1 4	3 1 9	3 3 3	3 1 0	3 2 9	3 0 2	3 0 4	3 1 2	3 1 3	3 1 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	A	A	A	+	A	+	+	+	A	+	+	M	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	M	A	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	A	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	A	A	A	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	+	A	M	A	A	A	+	A	+	A	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Hepatocellular carcinoma				X	X	X			X				X	X			X		X	X				X	
Hepatocellular adenoma										X							X								X
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma			X																						
Pancreas	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth											+														
Odontoma											X														
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Aorta, sarcoma			X																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Endocrine System																									
Adrenal cortex	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																X									
Parathyroid gland	M	+	+	+	+	M	+	M	+	+	+	+	M	M	+	M	M	+	+	+	M	M	M	M	+
Pituitary gland	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												X		X											X
Follicular cell, adenoma, multiple																									
General Body System																									
Tissue NOS			+									+													
Thoracic, sarcoma			X																						
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	31 18	32 2	32 7	33 2	33 5	34 2	34 8	35 3	35 8	36 9	37 1	37 7	38 1	38 3	38 5	38 8	39 0	39 1	39 6	40 0	40 1	40 3	40 4	40 5	40 9	41 0	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	38
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Hepatocellular carcinoma																											10
Hepatocellular adenoma		X	X	X		X	X	X	X			X	X							X	X	X			X	X	17
Hepatocellular adenoma, multiple					X																						1
Hepatocholangiocarcinoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tongue											+																1
Tooth																											1
Odontoma																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	47
Aorta, sarcoma																											1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X																								1
Carcinoma																											1
Parathyroid gland	M	M	+	M	M	M	+	M	+	M	+	M	M	M	+	+	+	M	+	+	M	M	+	M	+		25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X							X														5
Follicular cell, adenoma, multiple				X																							1
General Body System																											
Tissue NOS																											2
Thoracic, sarcoma																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma										X																	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	1 7 9	2 5 9	4 1 8	4 3 0	4 8 0	5 2 0	5 6 5	5 8 2	6 0 7	6 1 8	6 3 2	6 4 7	6 5 9	6 5 9	6 6 0	6 6 9	6 7 9	6 7 9	7 0 8	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 6	3 1 5	3 3 8	3 2 4	3 3 9	3 2 0	3 0 6	3 0 7	3 3 4	3 0 5	3 2 8	3 4 6	3 0 1	3 4 7	3 3 7	3 1 4	3 1 9	3 3 3	3 1 0	3 2 9	3 0 2	3 0 4	3 1 2	3 1 3	3 1 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+			+						+									
Pancreatic, carcinoma																X									
Lymph node, bronchial	M	M	+	M	M	M	M	+	M	M	+	M	+	M	M	M	+	M	+	M	M	+	M	M	M
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Sarcoma			X																						
Lymph node, mandibular	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mediastinal	M	M	+	+	+	M	+	M	M	M	M	M	M	+	+	M	+	M	M	M	M	M	+	+	+
Sarcoma			X																						
Spleen	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	M	M	M	M	M	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Sarcoma			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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X		X													X		X		X	X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																			X			X			
Hepatocellular carcinoma, metastatic, liver					X												X							X	
Hepatocholangiocarcinoma, metastatic, liver			X																						
Mediastinum, sarcoma			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																			+						
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	
Carcass ID Number	31 18	31 22	31 27	31 32	31 35	31 42	31 48	31 03	31 08	31 09	31 11	31 17	31 21	31 23	31 25	31 30	31 31	31 36	31 40	31 41	31 43	31 44	31 45	31 49	31 50	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Pancreatic, carcinoma																										1
Lymph node, bronchial	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	27
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	M	M	M	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M	M	+	M	M	+	+	+	25
Sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	34
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Sarcoma																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X		X	X				X				X				X		X		X	X				15
Alveolar/bronchiolar adenoma, multiple																									X	1
Alveolar/bronchiolar carcinoma																X										3
Hepatocellular carcinoma, metastatic, liver																										3
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	1 7 9	2 5 9	4 1 8	4 3 0	4 8 0	5 2 0	5 6 5	5 8 2	6 0 7	6 1 8	6 3 2	6 4 7	6 5 9	6 5 9	6 6 0	6 6 9	6 7 9	6 7 9	7 0 8	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 2 6	3 1 5	3 3 8	3 2 4	3 3 9	3 2 0	3 0 6	3 0 7	3 3 4	3 0 5	3 2 8	3 4 6	3 0 1	3 4 7	3 3 7	3 1 4	3 1 9	3 3 3	3 1 0	3 2 9	3 0 2	3 0 4	3 1 2	3 1 3	3 1 6
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																			X						
Ureter										+															
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic		X																							
Lymphoma malignant																				X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	3 1 8	3 2 2	3 2 7	3 3 2	3 3 5	3 4 2	3 4 8	3 0 3	3 0 8	3 0 9	3 1 1	3 1 7	3 2 1	3 2 3	3 2 5	3 3 0	3 3 1	3 3 6	3 4 0	3 4 1	3 4 3	3 4 4	3 4 5	3 4 9	3 5 0	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Lymphoma malignant															X											2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Harderian Gland: Adenoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate[b]	3.6%	8.0%	6.3%	0.0%
Terminal rate[c]	1/28 (4%)	2/36 (6%)	2/32 (6%)	0/30 (0%)
First incidence (days)	729 (T)	709	729 (T)	—[e]
Life table test[d]	P = 0.192N	P = 0.398	P = 0.547	P = 0.486N
Logistic regression test[d]	P = 0.182N	P = 0.375	P = 0.547	P = 0.486N
Cochran-Armitage test[d]	P = 0.183N			
Fisher exact test[d]		P = 0.309	P = 0.500	P = 0.500N
Liver: Hepatocellular Adenoma				
Overall rate	12/50 (24%)	16/50 (32%)	17/50 (34%)	18/50 (36%)
Adjusted rate	37.6%	39.1%	46.7%	55.8%
Terminal rate	9/28 (32%)	12/36 (33%)	13/32 (41%)	16/30 (53%)
First incidence (days)	522	360	579	618
Life table test	P = 0.142	P = 0.503	P = 0.324	P = 0.186
Logistic regression test	P = 0.182	P = 0.322	P = 0.329	P = 0.189
Cochran-Armitage test	P = 0.178			
Fisher exact test		P = 0.252	P = 0.189	P = 0.138
Liver: Hepatocellular Carcinoma				
Overall rate	17/50 (34%)	9/50 (18%)	13/50 (26%)	10/50 (20%)
Adjusted rate	41.1%	21.5%	28.5%	23.8%
Terminal rate	5/28 (18%)	5/36 (14%)	3/32 (9%)	1/30 (3%)
First incidence (days)	289	514	480	430
Life table test	P = 0.228N	P = 0.032N	P = 0.170N	P = 0.083N
Logistic regression test	P = 0.196N	P = 0.064N	P = 0.321N	P = 0.091N
Cochran-Armitage test	P = 0.200N			
Fisher exact test		P = 0.055N	P = 0.257N	P = 0.088N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	27/50 (54%)	24/50 (48%)	30/50 (60%)	27/50 (54%)
Adjusted rate	63.7%	54.9%	64.6%	66.7%
Terminal rate	13/28 (46%)	17/36 (47%)	16/32 (50%)	17/30 (57%)
First incidence (days)	289	360	480	430
Life table test	P = 0.413	P = 0.127N	P = 0.505N	P = 0.433N
Logistic regression test	P = 0.465	P = 0.321N	P = 0.389	P = 0.521N
Cochran-Armitage test	P = 0.447			
Fisher exact test		P = 0.345N	P = 0.343	P = 0.579N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	17/50 (34%)	10/50 (20%)	13/50 (26%)	10/50 (20%)
Adjusted rate	41.1%	24.1%	28.5%	23.8%
Terminal rate	5/28 (18%)	6/36 (17%)	3/32 (9%)	1/30 (3%)
First incidence (days)	289	514	480	430
Life table test	P = 0.202N	P = 0.049N	P = 0.170N	P = 0.083N
Logistic regression test	P = 0.167N	P = 0.101N	P = 0.321N	P = 0.091N
Cochran-Armitage test	P = 0.173N			
Fisher exact test		P = 0.088N	P = 0.257N	P = 0.088N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	27/50 (54%)	24/50 (48%)	30/50 (60%)	27/50 (54%)
Adjusted rate	63.7%	54.9%	64.6%	66.7%
Terminal rate	13/28 (46%)	17/36 (47%)	16/32 (50%)	17/30 (57%)
First incidence (days)	289	360	480	430
Life table test	P = 0.413	P = 0.127N	P = 0.505N	P = 0.433N
Logistic regression test	P = 0.465	P = 0.321N	P = 0.389	P = 0.521N
Cochran-Armitage test	P = 0.447			
Fisher exact test		P = 0.345N	P = 0.343	P = 0.579N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	5/50 (10%)	9/50 (18%)	10/50 (20%)	16/50 (32%)
Adjusted rate	15.1%	22.7%	27.4%	47.3%
Terminal rate	2/28 (7%)	6/36 (17%)	6/32 (19%)	13/30 (43%)
First incidence (days)	616	531	602	418
Life table test	P = 0.005	P = 0.341	P = 0.218	P = 0.014
Logistic regression test	P = 0.006	P = 0.234	P = 0.193	P = 0.009
Cochran-Armitage test	P = 0.006			
Fisher exact test		P = 0.194	P = 0.131	P = 0.006
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted rate	6.2%	2.8%	13.1%	9.6%
Terminal rate	1/28 (4%)	1/36 (3%)	2/32 (6%)	2/30 (7%)
First incidence (days)	610	729 (T)	588	708
Life table test	P = 0.341	P = 0.430N	P = 0.285	P = 0.534
Logistic regression test	P = 0.351	P = 0.474N	P = 0.227	P = 0.529
Cochran-Armitage test	P = 0.348			
Fisher exact test		P = 0.500N	P = 0.218	P = 0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/50 (14%)	10/50 (20%)	15/50 (30%)	19/50 (38%)
Adjusted rate	20.6%	25.2%	37.9%	55.0%
Terminal rate	3/28 (11%)	7/36 (19%)	8/32 (25%)	15/30 (50%)
First incidence (days)	610	531	588	418
Life table test	P = 0.004	P = 0.482	P = 0.114	P = 0.014
Logistic regression test	P = 0.004	P = 0.355	P = 0.064	P = 0.008
Cochran-Armitage test	P = 0.004			
Fisher exact test		P = 0.298	P = 0.045	P = 0.006
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted rate	10.7%	5.1%	3.1%	17.8%
Terminal rate	3/28 (11%)	1/36 (3%)	1/32 (3%)	4/30 (13%)
First incidence (days)	729 (T)	640	729 (T)	647
Life table test	P = 0.069	P = 0.390N	P = 0.257N	P = 0.294
Logistic regression test	P = 0.072	P = 0.437N	P = 0.257N	P = 0.278
Cochran-Armitage test	P = 0.073			
Fisher exact test		P = 0.500N	P = 0.309N	P = 0.243

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	4.8%	4.8%	8.4%	6.5%
Terminal rate	0/28 (0%)	1/36 (3%)	1/32 (3%)	1/30 (3%)
First incidence (days)	522	514	680	725
Life table test	P = 0.608	P = 0.655N	P = 0.564	P = 0.673N
Logistic regression test	P = 0.609N	P = 0.629	P = 0.474	P = 0.691
Cochran-Armitage test	P = 0.606N			
Fisher exact test		P = 0.691N	P = 0.500	P = 0.691N
All Organs: Benign Neoplasms				
Overall rate	20/50 (40%)	25/50 (50%)	26/50 (52%)	30/50 (60%)
Adjusted rate	56.4%	56.4%	68.1%	78.3%
Terminal rate	13/28 (46%)	17/36 (47%)	20/32 (63%)	22/30 (73%)
First incidence (days)	522	360	579	418
Life table test	P = 0.045	P = 0.564	P = 0.364	P = 0.100
Logistic regression test	P = 0.046	P = 0.304	P = 0.341	P = 0.053
Cochran-Armitage test	P = 0.046			
Fisher exact test		P = 0.211	P = 0.158	P = 0.036
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	15/50 (30%)	21/50 (42%)	16/50 (32%)
Adjusted rate	46.4%	35.2%	44.5%	36.4%
Terminal rate	5/28 (18%)	9/36 (25%)	7/32 (22%)	4/30 (13%)
First incidence (days)	289	514	480	259
Life table test	P = 0.349N	P = 0.082N	P = 0.381N	P = 0.184N
Logistic regression test	P = 0.287N	P = 0.179N	P = 0.448	P = 0.212N
Cochran-Armitage test	P = 0.309N			
Fisher exact test		P = 0.149N	P = 0.580N	P = 0.204N
All Organs: Benign or Malignant Neoplasms				
Overall rate	35/50 (70%)	34/50 (68%)	40/50 (80%)	41/50 (82%)
Adjusted rate	76.0%	70.8%	80.0%	89.0%
Terminal rate	17/28 (61%)	22/36 (61%)	22/32 (69%)	25/30 (83%)
First incidence (days)	289	360	480	259
Life table test	P = 0.131	P = 0.159N	P = 0.549N	P = 0.379
Logistic regression test	P = 0.069	P = 0.423N	P = 0.248	P = 0.162
Cochran-Armitage test	P = 0.063			
Fisher exact test		P = 0.500N	P = 0.178	P = 0.121

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposure group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at IIT Research Institute			
Isobutyl Nitrite	7/50	1/50	8/50
Overall Historical Incidence			
Total	141/947 (14.9%)	75/947 (7.9%)	205/947 (21.7%)
Standard deviation	7.0%	5.7%	8.0%
Range	6%-36%	0%-16%	10%-42%

[a] Data as of 12 May 1995

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1			1
Moribund	6	2	5	6
Natural deaths	15	12	13	13
Survivors				
Died last week of study			1	
Terminal sacrifice	28	36	31	30
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(33)	(39)	(37)	(38)
Epithelium, hyperplasia			1 (3%)	
Intestine small, duodenum	(45)	(48)	(43)	(45)
Parasite metazoan			1 (2%)	
Epithelium, hyperplasia			1 (2%)	1 (2%)
Intestine small, jejunum	(44)	(46)	(44)	(43)
Cyst		1 (2%)		
Epithelium, dysplasia		1 (2%)		
Peyer's patch, hyperplasia	1 (2%)	1 (2%)		
Intestine small, ileum	(42)	(46)	(44)	(41)
Peyer's patch, hyperplasia	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Basophilic focus	3 (6%)	3 (6%)	5 (10%)	4 (8%)
Clear cell focus	5 (10%)	4 (8%)	7 (14%)	3 (6%)
Cyst	1 (2%)	1 (2%)		
Eosinophilic focus	6 (12%)	8 (16%)	8 (16%)	12 (24%)
Eosinophilic focus, multiple	1 (2%)			
Fibrosis		1 (2%)		1 (2%)
Hemorrhage				2 (4%)
Hepatodiaphragmatic nodule			1 (2%)	
Inflammation, chronic		2 (4%)		
Mineralization			1 (2%)	
Mixed cell focus	3 (6%)	2 (4%)		1 (2%)
Necrosis	7 (14%)	8 (16%)	10 (20%)	10 (20%)
Thrombosis				1 (2%)
Hepatocyte, hyperplasia				1 (2%)
Hepatocyte, hypertrophy	1 (2%)			17 (34%)
Hepatocyte, necrosis	1 (2%)	1 (2%)	3 (6%)	10 (20%)
Hepatocyte, syncytial alteration		5 (10%)	8 (16%)	23 (46%)
Hepatocyte, vacuolization cytoplasmic	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Vein, thrombosis	1 (2%)		2 (4%)	
Pancreas	(49)	(50)	(48)	(48)
Inflammation	1 (2%)			
Acinus, hyperplasia				1 (2%)
Duct, cyst	1 (2%)	1 (2%)		
Duct, degeneration				1 (2%)
Duct, fibrosis	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Infiltration cellular	21 (42%)	26 (52%)	17 (34%)	20 (40%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Alimentary System (continued)				
Stomach, forestomach	(48)	(50)	(50)	(47)
Cyst				1 (2%)
Ulcer	1 (2%)			
Epithelium, hyperplasia				1 (2%)
Serosa, inflammation				1 (2%)
Stomach, glandular	(48)	(50)	(50)	(47)
Infiltration cellular	1 (2%)			
Inflammation			1 (2%)	
Metaplasia	1 (2%)			
Mineralization			2 (4%)	
Tongue				(1)
Inflammation, granulomatous				1 (100%)
Tooth			(1)	(1)
Developmental malformation			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	18 (36%)	36 (72%)	29 (58%)	25 (50%)
Inflammation	2 (4%)			
Myocardium, mineralization	1 (2%)			
Pericardium, hyperplasia	1 (2%)			
Endocrine System				
Adrenal cortex	(47)	(47)	(48)	(48)
Accessory adrenal cortical nodule	1 (2%)			
Degeneration	1 (2%)	2 (4%)	1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia	13 (28%)	8 (17%)	9 (19%)	4 (8%)
Vacuolization cytoplasmic	1 (2%)			
Capsule, hyperplasia	19 (40%)	22 (47%)	20 (42%)	17 (35%)
Adrenal medulla	(47)	(46)	(48)	(48)
Degeneration			1 (2%)	
Hyperplasia			2 (4%)	
Mineralization			1 (2%)	
Islets, pancreatic	(49)	(50)	(48)	(48)
Degeneration			1 (2%)	
Hyperplasia	5 (10%)	5 (10%)	8 (17%)	1 (2%)
Pituitary gland	(44)	(45)	(45)	(47)
Pars distalis, cyst		1 (2%)	2 (4%)	1 (2%)
Pars distalis, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicle, cyst			1 (2%)	
Follicular cell, hyperplasia	21 (42%)	21 (42%)	29 (58%)	32 (64%)
General Body System				
Tissue NOS	(2)	(3)	(1)	(2)
Cyst		1 (33%)		
Fat, necrosis		2 (67%)		1 (50%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Genital System				
Epididymis	(49)	(50)	(50)	(50)
Atypia cellular	1 (2%)	1 (2%)		
Cyst	1 (2%)			
Degeneration				2 (4%)
Fibrosis		1 (2%)		
Granuloma sperm	2 (4%)	1 (2%)	1 (2%)	
Infiltration cellular		1 (2%)		
Inflammation	1 (2%)			
Mineralization	1 (2%)			
Bilateral, fibrosis			1 (2%)	
Penis	(1)	(2)		
Concretion		1 (50%)		
Inflammation	1 (100%)	1 (50%)		
Preputial gland	(48)	(49)	(48)	(49)
Cyst			1 (2%)	
Degeneration	3 (6%)	3 (6%)	9 (19%)	6 (12%)
Degeneration, cystic		1 (2%)		
Fibrosis			1 (2%)	
Hyperplasia	1 (2%)		1 (2%)	
Infiltration cellular	1 (2%)	5 (10%)	6 (13%)	4 (8%)
Inflammation	6 (13%)	11 (22%)	11 (23%)	13 (27%)
Mineralization		1 (2%)		
Necrosis			1 (2%)	
Prostate	(46)	(49)	(50)	(50)
Atrophy	1 (2%)			
Infiltration cellular	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation	6 (13%)	5 (10%)	5 (10%)	6 (12%)
Seminal vesicle	(49)	(50)	(50)	(50)
Atrophy	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Degeneration	19 (39%)	26 (52%)	16 (32%)	22 (44%)
Inflammation	1 (2%)	1 (2%)	2 (4%)	
Testes	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		1 (2%)
Mineralization				1 (2%)
Germinal epithelium, atrophy		1 (2%)		
Germinal epithelium, degeneration				1 (2%)
Interstitial cell, hyperplasia		1 (2%)		
Tunic, fibrosis			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	1 (2%)			
Pigmentation, hemosiderin	2 (4%)	2 (4%)		1 (2%)
Myeloid cell, hyperplasia	2 (4%)	4 (8%)	9 (18%)	4 (8%)
Lymph node	(4)	(7)	(11)	(3)
Inguinal, hyperplasia	1 (25%)	1 (14%)		
Inguinal, pigmentation		1 (14%)		
Lumbar, congestion			1 (9%)	
Lumbar, hyperplasia	1 (25%)	4 (57%)	4 (36%)	2 (67%)
Lumbar, inflammation			2 (18%)	
Lumbar, pigmentation		1 (14%)		1 (33%)
Renal, congestion			2 (18%)	
Renal, hyperplasia		3 (43%)	3 (27%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(43)	(45)	(46)	(44)
Pigmentation, hemosiderin		1 (2%)		1 (2%)
Lymph node, mesenteric	(45)	(46)	(47)	(48)
Atrophy				1 (2%)
Congestion	1 (2%)	3 (7%)	1 (2%)	2 (4%)
Hematopoietic cell proliferation		3 (7%)		
Hyperplasia	1 (2%)	2 (4%)	3 (6%)	
Inflammation		2 (4%)		1 (2%)
Lymph node, mediastinal	(24)	(25)	(27)	(25)
Hyperplasia	1 (4%)			
Spleen	(50)	(50)	(49)	(49)
Atrophy	1 (2%)			
Hematopoietic cell proliferation	3 (6%)	4 (8%)	2 (4%)	
Lymphoid follicle, atrophy	2 (4%)		1 (2%)	1 (2%)
Lymphoid follicle, hyperplasia			2 (4%)	
Thymus	(37)	(37)	(39)	(34)
Atrophy	18 (49%)	11 (30%)	20 (51%)	11 (32%)
Cyst	1 (3%)			
Integumentary System				
Mammary gland	(3)	(2)	(3)	(3)
Atrophy	1 (33%)	1 (50%)	2 (67%)	1 (33%)
Skin	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Infiltration cellular, melanocyte		1 (2%)		
Inflammation	3 (6%)	6 (12%)	4 (8%)	3 (6%)
Necrosis	1 (2%)			
Ulcer	1 (2%)	5 (10%)	2 (4%)	3 (6%)
Hair follicle, atrophy		1 (2%)		
Prepuce, degeneration			1 (2%)	
Prepuce, hyperplasia, lymphoid			1 (2%)	
Prepuce, inflammation			2 (4%)	
Prepuce, ulcer			2 (4%)	
Sebaceous gland, cyst		1 (2%)		
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Vertebra, degeneration	1 (2%)			1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Mineralization	21 (42%)	18 (36%)	19 (38%)	19 (38%)
Respiratory System				
Larynx	(48)	(49)	(46)	(49)
Foreign body			1 (2%)	
Hemorrhage				1 (2%)
Infiltration, cellular	1 (2%)	4 (8%)	4 (9%)	
Glands, degeneration		1 (2%)	3 (7%)	2 (4%)
Glands, inflammation		1 (2%)	2 (4%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Respiratory System (continued)				
Lung	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Hemorrhage				1 (2%)
Infiltration cellular, histiocyte	2 (4%)		1 (2%)	2 (4%)
Inflammation	1 (2%)			
Pigmentation, hemosiderin			1 (2%)	
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)	5 (10%)	2 (4%)	4 (8%)
Alveolar epithelium, metaplasia		1 (2%)	2 (4%)	6 (12%)
Nose	(50)	(50)	(50)	(50)
Edema				1 (2%)
Hemorrhage	1 (2%)			1 (2%)
Inflammation	7 (14%)	3 (6%)	4 (8%)	1 (2%)
Polyp, inflammatory	2 (4%)	1 (2%)	2 (4%)	
Nasolacrimal duct, inflammation	3 (6%)		1 (2%)	1 (2%)
Respiratory epithelium, inflammation				1 (2%)
Respiratory epithelium, metaplasia, squamous		1 (2%)		
Pleura				(1)
Trachea	(50)	(50)	(50)	(50)
Glands, cyst				1 (2%)
Glands, hemorrhage				1 (2%)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Degeneration	1 (2%)			
Infarct	1 (2%)			
Inflammation	3 (6%)	5 (10%)	5 (10%)	3 (6%)
Metaplasia, osseous		1 (2%)		
Mineralization		1 (2%)		
Nephropathy	34 (68%)	38 (76%)	40 (80%)	36 (72%)
Pigmentation, bile	1 (2%)			
Cortex, cyst	1 (2%)	8 (16%)	5 (10%)	4 (8%)
Papilla, inflammation	3 (6%)	4 (8%)	3 (6%)	2 (4%)
Papilla, necrosis			1 (2%)	
Pelvis, dilatation	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Renal tubule, vacuolization cytoplasmic			1 (2%)	
Ureter			(2)	(1)
Degeneration			1 (50%)	1 (100%)
Inflammation			1 (50%)	
Urinary bladder	(48)	(50)	(49)	(49)
Calculus, microscopic observation only	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Infiltration cellular			1 (2%)	1 (2%)
Inflammation	7 (15%)	12 (24%)	6 (12%)	8 (16%)
Ulcer		1 (2%)		
Muscularis, inflammation			1 (2%)	
Muscularis, necrosis			1 (2%)	
Serosa, fibrosis			1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF ETHYLBENZENE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1		1	
Moribund	5	6	1	4
Natural deaths	9	6	8	9
Survivors				
Died last week of study	1			
Terminal sacrifice	34	38	40	37
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(48)	(48)	(50)	(50)
Gallbladder	(44)	(44)	(44)	(46)
Intestine large, rectum	(49)	(48)	(49)	(47)
Intestine large, cecum	(49)	(47)	(48)	(44)
Intestine small, duodenum	(45)	(48)	(47)	(46)
Polyp adenomatous			1 (2%)	
Intestine small, jejunum	(46)	(46)	(46)	(45)
Intestine small, ileum	(47)	(47)	(47)	(46)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma		1 (2%)		
Fibrosarcoma, metastatic, pancreas	1 (2%)			
Hemangioma		1 (2%)		
Hepatocellular carcinoma	7 (14%)	4 (8%)	3 (6%)	10 (20%)
Hepatocellular carcinoma, multiple				2 (4%)
Hepatocellular adenoma	6 (12%)	8 (16%)	9 (18%)	12 (24%)
Hepatocellular adenoma, multiple		1 (2%)	3 (6%)	4 (8%)
Pancreas	(50)	(50)	(50)	(49)
Fibrosarcoma	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(48)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(49)	(48)	(50)
Serosa, sarcoma, metastatic, uterus		1 (2%)		
Cardiovascular System				
Blood vessel	(46)	(48)	(48)	(50)
Adventitia, hepatocellular carcinoma, metastatic, liver	1 (2%)			
Heart	(50)	(49)	(50)	(50)
Fibrosarcoma, metastatic, pancreas	1 (2%)			
Endocrine System				
Adrenal cortex	(47)	(50)	(50)	(49)
Adenoma			1 (2%)	
Adrenal medulla	(47)	(50)	(50)	(49)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign		1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Endocrine System (continued)				
Pituitary gland	(48)	(49)	(47)	(49)
Pars distalis, adenoma	4 (8%)	8 (16%)	7 (15%)	5 (10%)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	5 (10%)	4 (8%)	3 (6%)	4 (8%)
Follicular cell, adenoma, multiple		2 (4%)		
General Body System				
Tissue NOS	(1)	(6)	(4)	(1)
Hemangiosarcoma		1 (17%)		
Leiomyosarcoma	1 (100%)			
Abdominal, osteosarcoma		1 (17%)		
Pelvic, sarcoma			1 (25%)	
Genital System				
Clitoral gland	(41)	(47)	(48)	(48)
Fibrosarcoma				1 (2%)
Ovary	(49)	(50)	(49)	(49)
Cystadenoma	2 (4%)			2 (4%)
Fibrosarcoma, metastatic, pancreas	1 (2%)			
Granulosa cell tumor benign	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)			
Polyp stromal	2 (4%)	1 (2%)	1 (2%)	
Sarcoma		1 (2%)		
Endometrium, adenoma	1 (2%)			
Myometrium, hemangioma			1 (2%)	
Vagina	(1)			
Leiomyosarcoma	1 (100%)			
Hematopoietic System				
Bone marrow	(48)	(50)	(50)	(50)
Lymph node	(3)	(7)	(2)	(5)
Iliac, hemangioma		1 (14%)		
Lumbar, osteosarcoma, metastatic, tissue NOS		1 (14%)		
Renal, hemangiosarcoma		1 (14%)		
Lymph node, bronchial	(32)	(40)	(29)	(38)
Fibrosarcoma, metastatic, pancreas	1 (3%)			
Hepatocellular carcinoma, metastatic, liver	1 (3%)			
Lymph node, mandibular	(47)	(48)	(47)	(44)
Lymph node, mesenteric	(48)	(48)	(46)	(44)
Fibrosarcoma, metastatic, pancreas	1 (2%)			
Lymph node, mediastinal	(34)	(42)	(41)	(31)
Fibrosarcoma, metastatic, pancreas	1 (3%)			
Hepatocellular carcinoma, metastatic, liver	1 (3%)			
Spleen	(50)	(50)	(50)	(49)
Capsule, fibrosarcoma, metastatic, pancreas	1 (2%)			
Thymus	(42)	(44)	(45)	(46)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Integumentary System				
Mammary gland	(49)	(50)	(48)	(49)
Carcinoma	1 (2%)	3 (6%)		
Skin	(50)	(50)	(49)	(50)
Fibroma				1 (2%)
Fibrosarcoma		2 (4%)		
Fibrous histiocytoma				1 (2%)
Hemangioma		1 (2%)	2 (4%)	
Squamous cell carcinoma		1 (2%)		
Sebaceous gland, adenoma			1 (2%)	
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Rib, sarcoma, metastatic, tissue NOS			1 (2%)	
Vertebra, osteosarcoma			1 (2%)	
Skeletal muscle		(2)		
Carcinoma, metastatic, mammary gland		1 (50%)		
Rhabdomyosarcoma		1 (50%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cerebrum, oligodendroglioma benign	1 (2%)			
Respiratory System				
Larynx	(49)	(49)	(47)	(48)
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	4 (8%)	4 (8%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)		1 (2%)	
Alveolar/bronchiolar carcinoma		2 (4%)		
Carcinoma, metastatic, harderian gland	1 (2%)			
Carcinoma, metastatic, mammary gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Osteosarcoma, metastatic, tissue NOS		1 (2%)		
Sarcoma, metastatic, tissue NOS			1 (2%)	
Sarcoma, metastatic, uterus		1 (2%)		
Squamous cell carcinoma, metastatic, lacrimal gland				1 (2%)
Nose	(49)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Pleura	(1)			
Hepatocellular carcinoma, metastatic, liver	1 (100%)			
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(1)		(1)	(3)
Adenoma			1 (100%)	3 (100%)
Carcinoma	1 (100%)			
Lacrimal gland				(1)
Squamous cell carcinoma				1 (100%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Cortex, fibrosarcoma, metastatic, pancreas	1 (2%)			
Ureter		(1)		(1)
Urinary bladder	(47)	(48)	(47)	(49)
Serosa, sarcoma, metastatic, uterus		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia granulocytic	1 (2%)			
Lymphoma malignant	3 (6%)	6 (12%)	5 (10%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	29	38	31	38
Total primary neoplasms	44	58	50	60
Total animals with benign neoplasms	20	26	27	28
Total benign neoplasms	27	34	39	40
Total animals with malignant neoplasms	13	20	9	18
Total malignant neoplasms	17	24	11	20
Total animals with metastatic neoplasms	5	5	3	2
Total metastatic neoplasms	18	9	4	2

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control

Number of Days on Study	2 1 5	4 2 3	5 0 1	5 6 5	5 7 8	5 9 2	5 9 7	6 1 8	6 2 9	6 3 9	6 6 8	6 9 4	7 1 5	7 1 8	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 0	0 9 7	0 9 0	0 6 4	0 6 7	0 9 2	0 7 5	0 9 4	0 7 3	0 6 5	0 6 0	0 9 9	0 6 6	0 7 7	0 5 8	0 5 6	0 7 1	0 7 6	0 7 9	0 9 5	0 5 1	0 5 2	0 5 5	0 5 9	0 6 1
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	A	+	+	+	M	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	M	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, pancreas													X												
Hepatocellular carcinoma				X							X		X	X					X				X		
Hepatocellular adenoma																	X	X							
Mesentery																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M
Adventitia, hepatocellular carcinoma, metastatic, liver														X											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, pancreas													X												
Endocrine System																									
Adrenal cortex	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	M	+	+	+	M	M	M	M	M	+
Pituitary gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X	X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												X				X		X							
General Body System																									
Tissue NOS				+																					
Leiomyosarcoma				X																					
Genital System																									
Clitoral gland	+	+	M	+	M	+	+	+	+	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X		X		
Fibrosarcoma, metastatic, pancreas													X												
Granulosa cell tumor benign																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 0 6 2	0 0 6 8	0 0 6 9	0 0 7 2	0 0 7 8	0 0 8 2	0 0 8 4	0 0 8 5	0 0 8 6	0 0 8 9	0 0 9 3	0 0 5 3	0 0 5 4	0 0 5 7	0 0 6 3	0 0 7 0	0 0 7 4	0 0 8 1	0 0 8 3	0 0 8 7	0 0 8 8	0 0 9 1	0 0 9 6	0 0 9 8	1 0 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, pancreas																										1
Hepatocellular carcinoma				X																						7
Hepatocellular adenoma										X					X	X							X			6
Mesentery															+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adventitia, hepatocellular carcinoma, metastatic, liver																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, pancreas																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	M	+	M	M	M	M	M	M	+	+	M	M	M	M	+	+	+	M	+	+	+	26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma																							X		X	4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma								X														X				5
General Body System																										
Tissue NOS																										1
Leiomyosarcoma																										1
Genital System																										
Clitoral gland	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										2
Fibrosarcoma, metastatic, pancreas																										1
Granulosa cell tumor benign															X											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	2 1 5	4 2 3	5 0 1	5 6 5	5 7 8	5 9 2	5 9 7	6 1 8	6 2 9	6 3 9	6 8 8	6 9 4	7 1 5	7 1 8	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 0	0 9 7	0 9 0	0 6 4	0 6 7	0 9 2	0 7 5	0 9 4	0 7 3	0 6 5	0 6 0	0 9 9	0 6 6	0 7 7	0 5 8	0 5 6	0 7 1	0 7 6	0 7 9	0 9 5	0 5 1	0 5 2	0 5 5	0 5 9	0 6 1
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma				X																					
Polyp stromal				X																			X		
Endometrium, adenoma																									
Vagina					+																				
Leiomyosarcoma					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+		+																		
Lymph node, bronchial	M	+	M	+	M	+	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	+	M
Fibrosarcoma, metastatic, pancreas													X												
Hepatocellular carcinoma, metastatic, liver														X											
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, pancreas													X												
Lymph node, mediastinal	M	+	+	M	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Fibrosarcoma, metastatic, pancreas													X												
Hepatocellular carcinoma, metastatic, liver														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, fibrosarcoma, metastatic, pancreas													X												
Thymus	M	+	+	+	M	+	M	M	M	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+
Hepatocellular carcinoma, metastatic, liver														X											
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, oligodendroglioma benign					X																				
Spinal cord							+																		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar adenoma, multiple																									
Carcinoma, metastatic, harderian, gland										X															
Hepatocellular carcinoma, metastatic, liver											X			X									X		
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland										X															
Pleura														+											
Hepatocellular carcinoma, metastatic, liver														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 0 6 2	0 0 6 8	0 0 6 9	0 0 7 2	0 0 7 8	0 0 8 2	0 0 8 4	0 0 8 5	0 0 8 6	0 0 8 9	0 0 9 3	0 0 5 3	0 0 5 4	0 0 5 7	0 0 6 3	0 0 7 0	0 0 7 4	0 0 8 1	0 0 8 3	0 0 8 7	0 0 8 8	0 0 9 1	0 0 9 6	0 0 9 8	0 1 0 0	Total Tissues/ Tumors
Genital System (continued)																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal																										2
Endometrium, adenoma																				X						1
Vagina																										1
Leiomyosarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																										3
Lymph node, bronchial	+	M	+	M	+	M	+	+	+	+	M	+	+	M	+	M	+	M	+	+	+	+	+	M	M	32
Fibrosarcoma, metastatic, pancreas																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, pancreas																										1
Lymph node, mediastinal	M	+	M	M	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	34
Fibrosarcoma, metastatic, pancreas																										1
Hepatocellular carcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, fibrosarcoma, metastatic, pancreas																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hepatocellular carcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma								X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cerebrum, oligodendroglioma benign																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X												X		3
Alveolar/bronchiolar adenoma, multiple																X										1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Pleura																										1
Hepatocellular carcinoma, metastatic, liver																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	2 1 5	4 2 3	5 0 1	5 6 5	5 7 8	5 9 2	5 9 7	6 1 8	6 2 9	6 3 9	6 8 8	6 9 4	7 1 5	7 1 8	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 8 0	0 9 7	0 9 0	0 6 4	0 6 7	0 9 2	0 7 5	0 9 4	0 7 3	0 6 5	0 6 0	0 9 9	0 6 6	0 7 7	0 5 8	0 5 6	0 7 1	0 7 6	0 7 9	0 9 5	0 5 1	0 5 2	0 5 5	0 5 9	0 6 1
Special Senses System																									
Harderian gland										+															
Carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, fibrosarcoma, metastatic, pancreas													X												
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic						X																			
Lymphoma malignant		X							X										X						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: Chamber Control
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 6 2	0 6 8	0 6 9	0 7 2	0 7 8	0 8 2	0 8 4	0 8 5	0 8 6	0 8 9	0 9 3	0 5 3	0 5 4	0 5 7	0 6 3	0 7 0	0 7 4	0 8 1	0 8 3	0 8 7	0 8 8	0 9 1	0 9 6	0 9 8	1 0 0	Total Tissues/ Tumors
Special Senses System																										
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, fibrosarcoma, metastatic, pancreas																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
Lymphoma malignant																										3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm

Number of Days on Study	3 0 0	4 9 5	5 6 2	5 8 4	5 9 0	6 0 2	6 3 9	6 4 2	6 9 7	6 9 7	7 0 3	7 2 3	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 5 2	1 5 3	1 8 7	1 8 8	1 5 5	1 6 1	1 9 4	1 9 6	1 7 8	1 8 3	1 6 7	1 8 4	1 6 0	1 7 1	1 7 7	1 5 1	1 5 4	1 5 7	1 6 6	1 6 9	1 7 0	1 7 2	1 7 4	1 7 6	1 8 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma					X																				
Hemangioma															X										
Hepatocellular carcinoma						X						X													
Hepatocellular adenoma			X								X							X					X		
Hepatocellular adenoma, multiple																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X										X												
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, sarcoma, metastatic, uterus		X																							
Cardiovascular System																									
Blood vessel	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	M	M	+	+	M	M	+	M	M	M	+	+	M	+	M	M	M	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X		X											X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																				X					
Follicular cell, adenoma, multiple									X							X									
General Body System																									
Tissue NOS			+		+											+									
Hemangiosarcoma																									
Abdominal, osteosarcoma			X																						
Genital System																									
Clitoral gland	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma		X																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 8 6	1 8 9	1 9 3	1 9 5	1 9 8	1 9 9	2 0 0	1 5 6	1 5 8	1 5 9	1 6 2	1 6 3	1 6 4	1 6 5	1 6 8	1 7 3	1 7 5	1 7 9	1 8 0	1 8 1	1 8 2	1 9 0	1 9 1	1 9 2	1 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										1
Hemangioma																										1
Hepatocellular carcinoma																	X					X				4
Hepatocellular adenoma			X	X								X					X									8
Hepatocellular adenoma, multiple		X																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, sarcoma, metastatic, uterus																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	M	M	M	+	+	M	+	+	M	M	M	+	+	M	M	M	+	M	M	+	M	24
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma									X		X					X				X						8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X									X	X											4
Follicular cell, adenoma, multiple																										2
General Body System																										
Tissue NOS			+								+						+									6
Hemangiosarcoma																	X									1
Abdominal, osteosarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X																			1
Sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	3 0 0	4 9 5	5 6 2	5 8 4	5 9 0	6 0 2	6 3 9	6 4 2	6 9 7	6 9 7	7 0 3	7 2 3	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 5 2	1 5 3	1 8 7	1 8 8	1 5 5	1 6 1	1 9 4	1 9 6	1 7 8	1 8 3	1 6 7	1 8 4	1 6 0	1 7 1	1 7 7	1 5 1	1 5 4	1 5 7	1 6 6	1 6 9	1 7 0	1 7 2	1 7 4	1 7 6	1 8 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+			+				+			+		+									
Iliac, hemangioma																									
Lumbar, osteosarcoma, metastatic, tissue NOS			X																						
Renal, hemangiosarcoma																									
Lymph node, bronchial	+	+	+	+	+	M	+	+	M	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	M	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X				X		X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma															X										
Hemangioma																					X				
Squamous cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+		+													
Carcinoma, metastatic, mammary gland												X													
Rhabdomyosarcoma										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X		X		
Alveolar/bronchiolar carcinoma					X																				
Carcinoma, metastatic, mammary gland								X																	
Hepatocellular carcinoma, metastatic, liver												X													
Osteosarcoma, metastatic, tissue NOS			X																						
Sarcoma, metastatic, uterus		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma, metastatic, liver					X																				
Ureter							+																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+
Serosa, sarcoma, metastatic, uterus		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X			X			X				X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 75 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 8 6	1 8 9	1 9 3	1 9 5	1 9 8	1 9 9	2 0 0	1 5 6	1 5 8	1 5 9	1 6 2	1 6 3	1 6 4	1 6 5	1 6 8	1 7 3	1 7 5	1 7 9	1 8 0	1 8 1	1 8 2	1 9 0	1 9 1	1 9 2	1 9 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+															7
Iliac, hemangioma											X															1
Lumbar, osteosarcoma, metastatic, tissue NOS																										1
Renal, hemangiosarcoma											X															1
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M	+	40
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma			X																							2
Hemangioma																										1
Squamous cell carcinoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Carcinoma, metastatic, mammary gland																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X											X			4
Alveolar/bronchiolar carcinoma																		X								2
Carcinoma, metastatic, mammary gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, tissue NOS																										1
Sarcoma, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma, metastatic, liver																										1
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Serosa, sarcoma, metastatic, uterus																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X					X																			6

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm

Number of Days on Study	0 8 6	4 3 7	4 4 6	6 5 9	6 8 2	6 9 4	7 0 1	7 0 5	7 0 7	7 0 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 6 8	2 7 9	2 6 0	2 9 4	2 7 4	2 9 3	2 8 5	2 8 6	2 8 0	2 7 6	2 7 2	2 7 3	2 8 4	2 9 9	2 5 1	2 5 2	2 5 5	2 5 6	2 5 8	2 5 9	2 6 5	2 6 6	2 6 7	2 7 1	2 7 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	M	A	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																					X				
Intestine small, jejunum	A	+	+	+	+	+	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X										
Hepatocellular adenoma				X				X														X			X
Hepatocellular adenoma, multiple					X														X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X																					
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	+	+	M	+	+	+	+	M	M	+	+	+	+	M	M	+	M	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma				X				X			X						X								
Pars intermedia, adenoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma					X																				
General Body System																									
Tissue NOS			+								+													+	
Pelvic, sarcoma			X																						
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Myometrium, hemangioma				X																					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	27 78	28 81	28 83	28 88	28 89	29 90	29 91	29 92	29 97	30 00	25 03	25 54	25 57	26 61	26 62	26 63	26 64	26 66	27 00	27 75	28 82	28 87	29 95	29 96	29 98	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma														X								X				3
Hepatocellular adenoma																	X	X		X			X	X		9
Hepatocellular adenoma, multiple												X														3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																						X				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Parathyroid gland	M	+	+	M	+	M	+	+	M	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	34
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma				X		X														X						7
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X	X																					3
General Body System																										
Tissue NOS																			+							4
Pelvic, sarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																									X	1
Myometrium, hemangioma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	0 8 6	4 3 7	4 4 6	6 5 9	6 8 2	6 9 4	7 0 1	7 0 5	7 0 7	7 0 8	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 6 8	2 7 9	2 6 0	2 9 4	2 7 4	2 9 3	2 8 5	2 8 6	2 8 0	2 7 6	2 7 2	2 7 3	2 8 4	2 9 9	2 9 1	2 5 2	2 5 5	2 5 6	2 5 8	2 5 9	2 6 5	2 6 6	2 6 7	2 7 1	2 7 7
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+																
Lymph node, bronchial	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	M	M	M	M	M	+	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	A	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Sebaceous gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rib, sarcoma, metastatic, tissue NOS			X																						
Vertebra, osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	M	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X					X	X														
Alveolar/bronchiolar adenoma, multiple							X																		
Hepatocellular carcinoma, metastatic, liver															X										
Sarcoma, metastatic, tissue NOS			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant		X		X	X				X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 250 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 7 8	2 8 1	2 8 3	2 8 8	2 8 9	2 9 0	2 9 1	2 9 2	2 9 7	3 0 0	2 5 3	2 5 4	2 5 7	2 6 1	2 6 2	2 6 3	2 6 4	2 6 6	2 7 0	2 7 5	2 8 2	2 8 7	2 9 5	2 9 6	2 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																				+						2
Lymph node, bronchial	+	M	M	+	+	+	M	M	M	+	+	+	M	+	M	+	+	M	+	M	M	+	+	M	+	29
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma									X															X		2
Sebaceous gland, adenoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rib, sarcoma, metastatic, tissue NOS																										1
Vertebra, osteosarcoma														X												1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																			X							4
Alveolar/bronchiolar adenoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																						X				2
Sarcoma, metastatic, tissue NOS																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																				+						1
Adenoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																				X						5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm

Number of Days on Study	0 7	1 6	5 6	6 1	6 1	6 6	6 8	7 1	7 1	7 1	7 1	7 1	7 2	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3
	9	8	2	4	6	1	1	2	2	3	8	3	0	0	0	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	3 7 2	3 8 0	3 8 4	3 5 9	3 6 3	4 0 0	3 5 6	3 6 1	3 5 8	3 6 9	3 7 0	3 6 0	3 9 6	3 5 1	3 9 3	3 9 5	3 5 4	3 5 5	3 6 2	3 7 5	3 7 7	3 7 8	3 7 9	3 8 2	3 8 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	M	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	M	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X	X	X						X	X					X
Hepatocellular carcinoma, multiple				X						X															
Hepatocellular adenoma					X										X			X			X				
Hepatocellular adenoma, multiple																X									
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	M	M	+	M	M	+	+	M	M	M	+	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																				X		X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma														X		X									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+				+	+												+						
Lymph node, bronchial	M	M	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	A	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node, mediastinal	M	M	M	+	M	+	+	M	M	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 8 5	3 8 6	3 8 7	3 8 8	3 9 1	3 9 4	3 9 9	3 5 2	3 5 3	3 5 5	3 6 4	3 6 5	3 6 6	3 6 7	3 6 8	3 7 1	3 7 3	3 7 4	3 7 6	3 8 1	3 8 9	3 9 0	3 9 2	3 9 7	3 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X								X						X						X			10
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X			X	X								X				X				X	X		X		12
Hepatocellular adenoma, multiple										X						X							X			4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	M	M	M	+	M	+	+	+	+	M	M	M	+	+	+	+	M	M	M	M	M	+	M	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma										X															X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma											X					X										4
General Body System																										
Tissue NOS				+																						1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma														X												2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																									5
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	38
Lymph node, mandibular	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Lymph node, mediastinal	+	M	M	+	+	+	+	M	M	+	+	+	M	M	M	+	M	+	M	+	M	+	+	+	+	31
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	0 7	1 9	5 6	6 1	6 4	6 6	6 8	7 1	7 1	7 2	7 2	7 3	7 1	7 2	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3	7 3
Carcass ID Number	3 7 2	3 8 0	3 8 4	3 5 9	3 6 3	4 0 0	3 5 6	3 6 1	3 5 8	3 6 9	3 7 0	3 6 0	3 9 6	3 5 1	3 9 3	3 9 5	3 5 4	3 5 5	3 6 2	3 7 5	3 7 7	3 7 8	3 7 9	3 8 2	3 8 3
Integumentary System																									
Mammary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X											
Fibrous histiocytoma																					X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X					X					X	
Hepatocellular carcinoma, metastatic, liver													X												
Squamous cell carcinoma, metastatic, lacrimal gland												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																							+		
Adenoma																							X		
Lacrimal gland												+													
Squamous cell carcinoma												X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter						+																			
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X	X												X	X					

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Ethylbenzene: 750 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	38505	38606	38707	38808	39101	39404	39909	39502	39553	39757	39964	40065	40166	40267	40368	40471	40773	40874	40976	41076	41181	41289	41390	41497	41598	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Fibrous histiocytoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X							X						X				X		X			8
Hepatocellular carcinoma, metastatic, liver																										1
Squamous cell carcinoma, metastatic, lacrimal gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																	+			+						3
Adenoma																	X			X						3
Lacrimal gland																										1
Squamous cell carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X																									5

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene

	Chamber Control	75 ppm	250 ppm	750 ppm
Harderian Gland: Adenoma				
Overall rate[a]	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate[b]	0.0%	0.0%	2.5%	8.1%
Terminal rate[c]	0/35 (0%)	0/38 (0%)	1/40 (3%)	3/37 (8%)
First incidence (days)	—[e]	—	730 (T)	730 (T)
Life table test[d]	P = 0.021	—[f]	P = 0.527	P = 0.131
Logistic regression test[d]	P = 0.021	—	P = 0.527	P = 0.131
Cochran-Armitage test[d]	P = 0.021			
Fisher exact test[d]		—	P = 0.500	P = 0.121
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	0.0%	2.5%	8.1%
Terminal rate	0/35 (0%)	0/38 (0%)	1/40 (3%)	3/37 (8%)
First incidence (days)	639	—	730 (T)	730 (T)
Life table test	P = 0.083	P = 0.486N	P = 0.730N	P = 0.330
Logistic regression test	P = 0.081	P = 0.516N	P = 0.761	P = 0.310
Cochran-Armitage test	P = 0.080			
Fisher exact test		P = 0.500N	P = 0.753N	P = 0.309
Liver: Hepatocellular Adenoma				
Overall rate	6/50 (12%)	9/50 (18%)	12/50 (24%)	16/50 (32%)
Adjusted rate	17.1%	22.1%	27.5%	41.8%
Terminal rate	6/35 (17%)	7/38 (18%)	9/40 (23%)	15/37 (41%)
First incidence (days)	730 (T)	562	659	614
Life table test	P = 0.013	P = 0.345	P = 0.165	P = 0.018
Logistic regression test	P = 0.014	P = 0.311	P = 0.128	P = 0.022
Cochran-Armitage test	P = 0.011			
Fisher exact test		P = 0.288	P = 0.096	P = 0.014
Liver: Hepatocellular Carcinoma				
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	12/50 (24%)
Adjusted rate	17.3%	9.7%	7.5%	28.3%
Terminal rate	3/35 (9%)	2/38 (5%)	3/40 (8%)	7/37 (19%)
First incidence (days)	565	602	730 (T)	612
Life table test	P = 0.029	P = 0.238N	P = 0.127N	P = 0.205
Logistic regression test	P = 0.022	P = 0.259N	P = 0.150N	P = 0.162
Cochran-Armitage test	P = 0.022			
Fisher exact test		P = 0.262N	P = 0.159N	P = 0.154
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	13/50 (26%)	12/50 (24%)	15/50 (30%)	25/50 (50%)
Adjusted rate	32.8%	28.2%	34.5%	57.9%
Terminal rate	9/35 (26%)	8/38 (21%)	12/40 (30%)	19/37 (51%)
First incidence (days)	565	562	659	612
Life table test	P = 0.004	P = 0.426N	P = 0.562	P = 0.029
Logistic regression test	P = 0.002	P = 0.478N	P = 0.471	P = 0.015
Cochran-Armitage test	P = 0.002			
Fisher exact test		P = 0.500N	P = 0.412	P = 0.011

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	5/49 (10%)	8/50 (16%)
Adjusted rate	10.9%	10.5%	11.4%	21.6%
Terminal rate	3/35 (9%)	4/38 (11%)	2/40 (5%)	8/37 (22%)
First incidence (days)	694	730 (T)	682	730 (T)
Life table test	P = 0.106	P = 0.598N	P = 0.579	P = 0.206
Logistic regression test	P = 0.111	P = 0.618N	P = 0.525	P = 0.218
Cochran-Armitage test	P = 0.096			
Fisher exact test		P = 0.643N	P = 0.487	P = 0.178
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	6/50 (12%)	5/49 (10%)	8/50 (16%)
Adjusted rate	10.9%	15.0%	11.4%	21.6%
Terminal rate	3/35 (9%)	5/38 (13%)	2/40 (5%)	8/37 (22%)
First incidence (days)	694	590	682	730 (T)
Life table test	P = 0.184	P = 0.419	P = 0.579	P = 0.206
Logistic regression test	P = 0.181	P = 0.386	P = 0.525	P = 0.218
Cochran-Armitage test	P = 0.169			
Fisher exact test		P = 0.370	P = 0.487	P = 0.178
Mammary Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.9%	7.3%	0.0%	0.0%
Terminal rate	1/35 (3%)	1/38 (3%)	0/40 (0%)	0/37 (0%)
First incidence (days)	730 (T)	642	—	—
Life table test	P = 0.144N	P = 0.336	P = 0.473N	P = 0.489N
Logistic regression test	P = 0.149N	P = 0.311	P = 0.473N	P = 0.489N
Cochran-Armitage test	P = 0.150N			
Fisher exact test		P = 0.309	P = 0.500N	P = 0.500N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	4/48 (8%)	8/49 (16%)	7/47 (15%)	5/49 (10%)
Adjusted rate	11.1%	19.8%	17.0%	13.5%
Terminal rate	3/35 (9%)	6/38 (16%)	5/38 (13%)	5/37 (14%)
First incidence (days)	725	697	659	730 (T)
Life table test	P = 0.445N	P = 0.223	P = 0.322	P = 0.533
Logistic regression test	P = 0.425N	P = 0.203	P = 0.276	P = 0.542
Cochran-Armitage test	P = 0.459N			
Fisher exact test		P = 0.188	P = 0.249	P = 0.513
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	5/50 (10%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rate	13.7%	15.2%	7.1%	10.8%
Terminal rate	4/35 (11%)	5/38 (13%)	2/40 (5%)	4/37 (11%)
First incidence (days)	694	697	682	730 (T)
Life table test	P = 0.355N	P = 0.557	P = 0.288N	P = 0.462N
Logistic regression test	P = 0.339N	P = 0.532	P = 0.320N	P = 0.449N
Cochran-Armitage test	P = 0.372N			
Fisher exact test		P = 0.500	P = 0.357N	P = 0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
All Organs: Hemangioma				
Overall rate	0/50 (0%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	7.9%	7.0%	0.0%
Terminal rate	0/35 (0%)	3/38 (8%)	2/40 (5%)	0/37 (0%)
First incidence (days)	—	730 (T)	659	—
Life table test	P = 0.280N	P = 0.136	P = 0.149	—
Logistic regression test	P = 0.281N	P = 0.136	P = 0.123	—
Cochran-Armitage test	P = 0.291N			
Fisher exact test		P = 0.121	P = 0.121	—
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	10.5%	7.0%	0.0%
Terminal rate	0/35 (0%)	4/38 (11%)	2/40 (5%)	0/37 (0%)
First incidence (days)	—	730 (T)	659	—
Life table test	P = 0.212N	P = 0.074	P = 0.149	—
Logistic regression test	P = 0.211N	P = 0.074	P = 0.123	—
Cochran-Armitage test	P = 0.222N			
Fisher exact test		P = 0.059	P = 0.121	—
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	6/50 (12%)	5/50 (10%)	5/50 (10%)
Adjusted rate	7.1%	13.4%	10.7%	12.2
Terminal rate	1/35 (3%)	2/38 (5%)	1/40 (3%)	3/37 (8%
First incidence (days)	423	300	437	666
Life table test	P = 0.496	P = 0.278	P = 0.416	P = 0.393
Logistic regression test	P = 0.237	P = 0.175	P = 0.340	P = 0.358
Cochran-Armitage test	P = 0.469			
Fisher exact test		P = 0.243	P = 0.357	P = 0.357
All Organs: Benign Neoplasms				
Overall rate	20/50 (40%)	26/50 (52%)	27/50 (54%)	28/50 (56%)
Adjusted rate	50.8%	63.2%	59.9%	71.6%
Terminal rate	16/35 (46%)	23/38 (61%)	22/40 (55%)	26/37 (70%)
First incidence (days)	565	562	659	614
Life table test	P = 0.163	P = 0.260	P = 0.284	P = 0.122
Logistic regression test	P = 0.176	P = 0.190	P = 0.163	P = 0.116
Cochran-Armitage test	P = 0.132			
Fisher exact test		P = 0.158	P = 0.115	P = 0.080
All Organs: Malignant Neoplasms				
Overall rate	13/50 (26%)	20/50 (40%)	9/50 (18%)	18/50 (36%)
Adjusted rate	28.5%	40.5%	19.3%	39.7%
Terminal rate	4/35 (11%)	9/38 (24%)	4/40 (10%)	10/37 (27%)
First incidence (days)	423	300	437	568
Life table test	P = 0.380	P = 0.181	P = 0.191N	P = 0.279
Logistic regression test	P = 0.075	P = 0.045	P = 0.265N	P = 0.192
Cochran-Armitage test	P = 0.322			
Fisher exact test		P = 0.101	P = 0.235N	P = 0.194

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Ethylbenzene (continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	29/50 (58%)	38/50 (76%)	31/50 (62%)	38/50 (76%)
Adjusted rate	62.9%	76.0%	64.5%	80.8%
Terminal rate	18/35 (51%)	26/38 (68%)	23/40 (58%)	28/37 (76%)
First incidence (days)	423	300	437	568
Life table test	P = 0.229	P = 0.187	P = 0.466N	P = 0.161
Logistic regression test	P = 0.042	P = 0.041	P = 0.431	P = 0.045
Cochran-Armitage test	P = 0.116			
Fisher exact test		P = 0.044	P = 0.419	P = 0.044

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposure group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposure group. The life table test regards neoplasms 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. For all tests, a negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE D4a
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at IIT Research Institute			
Isobutyl Nitrite	4/51	2/51	6/51
Overall Historical Incidence			
Total	61/939 (6.5%)	38/939 (4.1%)	97/939 (10.3%)
Standard deviation	3.2%	3.2%	3.7%
Range	0%-14%	0%-12%	0%-16%

[a] Data as of 12 May 1995

TABLE D4b
Historical Incidence of Hepatocellular Neoplasms in Chamber Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at IIT Research Institute			
Isobutyl Nitrite	6/51	4/51	10/51
Overall Historical Incidence			
Total	114/937 (12.2%)	103/937 (11.0%)	200/937 (21.3%)
Standard deviation	9.7%	6.7%	11.9%
Range	0%-40%	0%-30%	3%-54%

[a] Data as of 12 May 1995

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Ethylbenzene[a]

	Chamber Control	75 ppm	250 ppm	750 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	1		1	
Moribund	5	6	1	4
Natural deaths	9	6	8	9
Survivors				
Died last week of study	1			
Terminal sacrifice	34	38	40	37
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(44)	(44)	(44)	(46)
Infiltration cellular	1 (2%)			
Intestine small, duodenum	(45)	(48)	(47)	(46)
Ulcer				1 (2%)
Intestine small, jejunum	(46)	(46)	(46)	(45)
Peyer's patch, hyperplasia				1 (2%)
Intestine small, ileum	(47)	(47)	(47)	(46)
Peyer's patch, hyperplasia		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Basophilic focus	3 (6%)		4 (8%)	3 (6%)
Clear cell focus	1 (2%)		1 (2%)	
Eosinophilic focus	5 (10%)	7 (14%)	6 (12%)	22 (44%)
Hemorrhage			1 (2%)	1 (2%)
Hepatodiaphragmatic nodule			2 (4%)	
Infiltration cellular	3 (6%)			
Inflammation	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Mineralization				1 (2%)
Mixed cell focus			1 (2%)	1 (2%)
Necrosis	1 (2%)	4 (8%)	3 (6%)	4 (8%)
Pigmentation, hemosiderin	1 (2%)	1 (2%)		
Bile duct, cyst				1 (2%)
Hepatocyte, hypertrophy				1 (2%)
Hepatocyte, necrosis		1 (2%)		
Hepatocyte, syncytial alteration			1 (2%)	
Hepatocyte, vacuolization cytoplasmic	2 (4%)		2 (4%)	1 (2%)
Serosa, inflammation				1 (2%)
Mesentery	(2)			
Fat, necrosis	2 (100%)			
Pancreas	(50)	(50)	(50)	(49)
Angiectasis		1 (2%)		
Atrophy		2 (4%)		
Cyst		1 (2%)		
Degeneration		1 (2%)		
Fibrosis		1 (2%)		
Infiltration cellular	7 (14%)	12 (24%)	12 (24%)	10 (20%)
Necrosis		1 (2%)		
Acinus, hyperplasia	1 (2%)			
Duct, cyst				1 (2%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Alimentary System (continued)				
Salivary glands	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Infiltration cellular	30 (60%)	32 (64%)	33 (66%)	30 (60%)
Stomach, forestomach	(50)	(49)	(48)	(50)
Hyperplasia				2 (4%)
Ulcer			1 (2%)	
Epithelium, cyst				2 (4%)
Epithelium, hyperplasia		2 (4%)		1 (2%)
Stomach, glandular	(50)	(49)	(48)	(50)
Infiltration cellular	1 (2%)			
Glands, cyst	1 (2%)			
Glands, hyperplasia				1 (2%)
Serosa, infiltration cellular				1 (2%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	10 (20%)	23 (47%)	23 (46%)	15 (30%)
Endocrine System				
Adrenal cortex	(47)	(50)	(50)	(49)
Accessory adrenal cortical nodule	2 (4%)	1 (2%)		
Degeneration	12 (26%)	4 (8%)	4 (8%)	5 (10%)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Hyperplasia	3 (6%)	5 (10%)	3 (6%)	3 (6%)
Infiltration cellular		2 (4%)		
Inflammation		3 (6%)		
Necrosis	1 (2%)			
Vacuolization cytoplasmic	1 (2%)			
Capsule, hyperplasia	46 (98%)	49 (98%)	48 (96%)	46 (94%)
Adrenal medulla	(47)	(50)	(50)	(49)
Hemorrhage	1 (2%)			
Hyperplasia	2 (4%)	3 (6%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia		2 (4%)	2 (4%)	
Infiltration cellular	1 (2%)		2 (4%)	
Parathyroid gland	(26)	(24)	(34)	(27)
Infiltration cellular		1 (4%)		
Pituitary gland	(48)	(49)	(47)	(49)
Pars distalis, angiectasis			4 (9%)	2 (4%)
Pars distalis, cyst		1 (2%)		
Pars distalis, hemorrhage	3 (6%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia	10 (21%)	12 (24%)	23 (49%)	22 (45%)
Pars distalis, necrosis				1 (2%)
Pars intermedia, hyperplasia	2 (4%)	1 (2%)		1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular			1 (2%)	
Follicle, degeneration	1 (2%)			
Follicular cell, hyperplasia	18 (36%)	23 (46%)	25 (50%)	35 (70%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
General Body System				
Tissue NOS	(1)	(6)	(4)	(1)
Fat, necrosis		4 (67%)	3 (75%)	1 (100%)
Genital System				
Clitoral gland	(41)	(47)	(48)	(48)
Atrophy			1 (2%)	
Degeneration				1 (2%)
Ovary	(49)	(50)	(49)	(49)
Angiectasis	2 (4%)	1 (2%)		
Atrophy		1 (2%)	1 (2%)	
Cyst	8 (16%)	8 (16%)	10 (20%)	10 (20%)
Hemorrhage	1 (2%)		1 (2%)	
Infiltration cellular			2 (4%)	
Mineralization				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Degeneration	2 (4%)	1 (2%)		1 (2%)
Hemorrhage			1 (2%)	1 (2%)
Infiltration cellular				1 (2%)
Inflammation	3 (6%)			1 (2%)
Thrombosis			1 (2%)	
Endometrium, hyperplasia	44 (88%)	46 (92%)	47 (94%)	46 (92%)
Hematopoietic System				
Bone marrow	(48)	(50)	(50)	(50)
Hematopoietic cell proliferation		1 (2%)		
Infiltration cellular, histiocyte				1 (2%)
Inflammation	1 (2%)			
Myelofibrosis				2 (4%)
Pigmentation, hemosiderin	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Myeloid cell, hyperplasia	1 (2%)			1 (2%)
Lymph node	(3)	(7)	(2)	(5)
Iliac, hyperplasia		1 (14%)		
Inguinal, hyperplasia				1 (20%)
Inguinal, pigmentation, hemosiderin	1 (33%)			
Lumbar, hyperplasia	1 (33%)	2 (29%)		
Pancreatic, hyperplasia				1 (20%)
Renal, hyperplasia	1 (33%)			
Renal, necrosis		1 (14%)		
Lymph node, bronchial	(32)	(40)	(29)	(38)
Hyperplasia		2 (5%)	1 (3%)	2 (5%)
Lymph node, mandibular	(47)	(48)	(47)	(44)
Hyperplasia	1 (2%)	2 (4%)		2 (5%)
Lymph node, mesenteric	(48)	(48)	(46)	(44)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	4 (8%)	3 (6%)	3 (7%)	2 (5%)
Inflammation		2 (4%)		
Inflammation, granulomatous	1 (2%)	1 (2%)		
Necrosis		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Hematopoietic System (continued)				
Lymph node, mediastinal	(34)	(42)	(41)	(31)
Hyperplasia	3 (9%)	4 (10%)		2 (6%)
Hyperplasia, histiocytic	1 (3%)			
Spleen	(50)	(50)	(50)	(49)
Hematopoietic cell proliferation	4 (8%)	7 (14%)	2 (4%)	1 (2%)
Hyperplasia	1 (2%)			
Necrosis		1 (2%)		
Pigmentation, hemosiderin	4 (8%)	1 (2%)	1 (2%)	4 (8%)
Lymphoid follicle, hyperplasia	9 (18%)	5 (10%)	1 (2%)	3 (6%)
Thymus	(42)	(44)	(45)	(46)
Atrophy	5 (12%)	5 (11%)	5 (11%)	6 (13%)
Thymocyte, hyperplasia	1 (2%)	2 (5%)		
Integumentary System				
Mammary gland	(49)	(50)	(48)	(49)
Galactocele		1 (2%)	1 (2%)	
Hyperplasia		1 (2%)		
Skin	(50)	(50)	(49)	(50)
Fibrosis			1 (2%)	
Inflammation	1 (2%)		2 (4%)	
Necrosis	1 (2%)			
Ulcer	1 (2%)		2 (4%)	
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Arthrosis			1 (2%)	
Fracture		2 (4%)		
Periosteum, femur, inflammation	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)			
Mineralization	19 (38%)	17 (34%)	26 (52%)	25 (50%)
Cerebellum, atrophy	1 (2%)			
Cerebrum, atrophy	2 (4%)	1 (2%)	2 (4%)	
Cerebrum, gliosis				1 (2%)
Cerebrum, hemorrhage				1 (2%)
Medulla, atrophy	1 (2%)			
Medulla, hemorrhage	1 (2%)			
Meninges, infiltration cellular		2 (4%)	1 (2%)	
Spinal cord	(1)			
Hemorrhage	1 (100%)			
Myelin, degeneration	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Ethylbenzene
(continued)

	Chamber Control	75 ppm	250 ppm	750 ppm
Respiratory System				
Larynx	(49)	(49)	(47)	(48)
Degeneration			1 (2%)	
Infiltration cellular	1 (2%)		1 (2%)	1 (2%)
Glands, degeneration		2 (4%)	2 (4%)	2 (4%)
Glands, inflammation			1 (2%)	
Lung	(50)	(50)	(49)	(50)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, histiocyte	1 (2%)			
Alveolar epithelium, hyperplasia		1 (2%)	3 (6%)	1 (2%)
Alveolar epithelium, metaplasia				1 (2%)
Vein, thrombosis	1 (2%)			
Nose	(49)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Inflammation	3 (6%)	2 (4%)	3 (6%)	
Nasolacrimal duct, inflammation	1 (2%)			
Respiratory epithelium, metaplasia, squamous	2 (4%)		1 (2%)	
Pleura	(1)			
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Casts protein	1 (2%)			1 (2%)
Infiltration cellular		1 (2%)		
Mineralization				1 (2%)
Nephropathy	13 (26%)	7 (14%)	9 (18%)	21 (42%)
Cortex, cyst			1 (2%)	1 (2%)
Cortex, metaplasia, osseous		1 (2%)		
Urinary bladder	(47)	(48)	(47)	(49)
Hemorrhage	1 (2%)			
Infiltration cellular	4 (9%)	4 (8%)	4 (9%)	5 (10%)
Inflammation	1 (2%)			
Ulcer	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1988). Ethylbenzene was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA97, TA98, TA100, and TA1535) 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. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of ethylbenzene. The high dose was limited by toxicity. Trials performed in the absence of S9 were repeated. Trials initially performed with 10% S9 were repeated with 30% S9.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al*. (1988). Ethylbenzene was supplied as a coded aliquot by Radian Corporation. The high dose of 160 µg/mL was determined by toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine-resistant cells, subcultures were exposed to medium containing THMG (thymidine, hypoxanthine, methotrexate, and glycine) for 1 day, to medium containing THG (thymidine, hypoxanthine, and glycine) for 1 day, and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with ethylbenzene continued for 4 hours, at which time the medium plus ethylbenzene was removed and the cells were resuspended in 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, cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant ($TK^{-/-}$) cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was obtained, the test was not performed with S9.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al*. (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for ethylbenzene to be considered

positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al*. (1987). Ethylbenzene was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), 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-substituted DNA. Each test consisted of concurrent solvent and positive controls and of four doses of ethylbenzene; the high dose was limited by toxicity. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with ethylbenzene in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing ethylbenzene was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 1.5 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 ethylbenzene, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no ethylbenzene, and incubation proceeded for an additional 25.8 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of "equivocal."

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with ethylbenzene for 8.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with ethylbenzene and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 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.

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. One hundred first-division metaphase cells were scored at each dose level. 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).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a

single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay can be found in MacGregor *et al*. (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of a 13-week toxicity study (NTP, 1992). Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned at 630× or 1,000× to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in each animal of each dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 510 nm ultraviolet illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell. In addition, the percentage of PCEs among the total erythrocyte population was determined.

Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using Student's *t*-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test. The percentage of PCEs among total erythrocytes was analyzed by an analysis of variance on ranks (classed by sex), and individual dose groups were compared with the concurrent solvent control using a *t*-test on ranks.

RESULTS

Ethylbenzene was not mutagenic in *S. typhimurium* strain TA97, TA98, TA100, or TA1535 with or without Aroclor-induced rat or hamster liver S9 (Table E1; Zeiger *et al.*, 1988). A positive response was observed with ethylbenzene in the L5178Y mouse lymphoma cell assay in the absence of S9 at the highest nonlethal dose tested (80 µg/mL); the assay was not performed with S9 (Table E2; McGregor *et al.*, 1988). A significant amount of cytotoxicity was noted at this dose level (relative total growth was reduced to 34% and 13% of the control level in each of two trials). No increases in SCEs (Table E3) or Abs (Table E4) were induced by ethylbenzene in cultured CHO cells, with or without S9. *In vivo*, no increases in frequencies of micronucleated erythrocytes were observed in peripheral blood samples from male and female mice treated for 13 weeks with ethylbenzene (Table E5).

TABLE E1
Mutagenicity of Ethylbenzene in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
TA100							
	0	112 ± 9.3	147 ± 4.0	114 ± 8.2	136 ± 3.3	111 ± 2.1	154 ± 7.8
	10	104 ± 0.9	161 ± 5.8	120 ± 11.5	138 ± 9.5	100 ± 5.0	155 ± 9.0
	33	100 ± 4.4	147 ± 4.1	137 ± 22.7	140 ± 138	110 ± 8.1	155 ± 9.3
	100	97 ± 4.8	157 ± 3.2	109 ± 7.1	138 ± 12.2	105 ± 2.3	161 ± 14.5
	333	97 ± 6.9	118 ± 11.5	97 ± 7.1	137 ± 1.2	111 ± 4.7	127 ± 13.2
	666	76 ± 6.2	74 ± 4.0[c]				
	1,000			98 ± 1.7	112 ± 6.1	77 ± 8.2	109 ± 8.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		375 ± 12.3	394 ± 32.5	873 ± 46.0	740 ± 18.0	1,304 ± 306.0	352 ± 19.8
TA1535							
	0	14 ± 3.7	29 ± 3.8	7 ± 1.5	11 ± 2.3	9 ± 2.0	12 ± 1.2
	10	19 ± 1.3	26 ± 3.2	9 ± 1.3	14 ± 1.5	8 ± 0.7	13 ± 2.5
	33	21 ± 4.6	19 ± 2.5	6 ± 0.7	11 ± 1.5	9 ± 3.0	8 ± 0.6
	100	16 ± 1.5	25 ± 2.5	8 ± 1.5	10 ± 2.4	5 ± 0.6	10 ± 1.5
	333	16 ± 2.1	14 ± 0.3	9 ± 1.2	9 ± 2.7	8 ± 2.4	6 ± 0.9
	666	0 ± 0.0[e]	0 ± 0.0				
	1,000			5 ± 1.8	11 ± 1.9	5 ± 1.5	9 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		418 ± 23.1	520 ± 20.0	703 ± 16.5	431 ± 36.9	393 ± 72.0	101 ± 11.4
TA97							
	0	182 ± 1.5	111 ± 9.5	195 ± 12.3	184 ± 18.2	200 ± 10.0	218 ± 6.5
	10	203 ± 1.8	120 ± 16.3	194 ± 10.3	210 ± 22.5	190 ± 15.1	249 ± 20.2
	33	198 ± 6.9	144 ± 2.4	195 ± 3.5	186 ± 22.4	193 ± 5.3	227 ± 16.5
	100	195 ± 9.9	124 ± 5.2	191 ± 7.1	227 ± 1.8	179 ± 7.8	12 ± 13.0
	333	188 ± 5.7	108 ± 9.1	173 ± 3.5	202 ± 8.3	211 ± 3.3	211 ± 6.4
	666	103 ± 1.5	6 ± 5.7[c]				
	1,000			124 ± 9.6	180 ± 15.9	189 ± 23.4	195 ± 15.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		856 ± 20.8	954 ± 47.1	1,587 ± 146.1	1,123 ± 30.4	647 ± 154.3	540 ± 12.7
TA98							
	0	26 ± 1.8	29 ± 5.5	24 ± 3.2	35 ± 3.8	34 ± 3.3	34 ± 7.2
	10	16 ± 2.3	27 ± 4.4	29 ± 1.8	34 ± 4.7	26 ± 1.8	32 ± 4.1
	33	22 ± 4.8	35 ± 7.8	26 ± 0.6	34 ± 4.5	34 ± 3.5	32 ± 2.3
	100	21 ± 2.4	16 ± 2.1	28 ± 4.7	26 ± 1.2	32 ± 2.3	30 ± 4.2
	333	18 ± 1.5	20 ± 8.4	23 ± 3.0	30 ± 0.7	30 ± 2.3	28 ± 5.6
	666	13 ± 1.2	27 ± 14.5[c]				
	1,000			21 ± 2.3	30 ± 0.9	26 ± 1.5	30 ± 3.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		845 ± 69.2	566 ± 45.0	1,082 ± 174.8	285 ± 32.9	784 ± 214.8	149 ± 10.7

[a] Study was performed at SRI International. The detailed protocol and these data are presented in Zeiger *et al*. (1988). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[e] Precipitate on plate, toxic

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Ethylbenzene[a]

Compound	Concentration (µg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Dimethylsulfoxide[c]		84	94	159	63	
		89	106	150	56	
		78	108	155	66	
		87	92	138	53	60
Ethylmethane sulfonate[d]	250	81	85	357	147	
		83	95	374	150	149*
Methylmethane sulfonate[d]	15	61	40	251	138	
		52	39	238	152	145*
Ethylbenzene	10	81	103	123	51	
		86	106	157	61	56
	20	81	90	130	54	
		81	93	127	52	53
	40	87	82	175	67	
		73	72	144	66	67
	80	74	36	1,235	559	
		71	32	1,335	619	589*
	160	Lethal				
Trial 2						
Dimethylsulfoxide		85	106	87	34	
		69	95	63	30	
		82	98	75	30	
		100	101	91	30	31
Ethylmethane sulfonate	250	50	67	302	201	
		51	67	381	250	225*
Methylmethane sulfonate	15	43	34	122	94	
		42	32	152	120	107*
Ethylbenzene	20	83	83	109	44	
		82	83	102	41	42
	40	78	61	75	32	
		73	54	58	27	29
	60	64	37	91	48	
		68	60	79	39	43
	80	48	10	228	159	
		55	15	233	142	150*
	100	Lethal				

* Significant positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Inveresk Research International. The detailed protocol and these data are presented in McGregor *et al*. (1988).
[b] Mutant fraction (MF) (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 [to arrive at MF/10^6 cells treated]).
[c] Solvent control
[d] Positive control

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Ethylbenzene[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Summary: Negative								
Dimethylsulfoxide[c]		50	1,045	555	0.53	11.1	25.5	
Mitomycin-C[d]	0.001	50	1,041	773	0.74	15.5	25.5	39.81
	0.010	5	103	220	2.13	44.0	25.5	302.17
Ethylbenzene	75.5	50	1,046	551	0.52	11.0	25.5	−0.82
	99.5	50	1,049	522	0.49	10.4	25.5	−6.31
	125[e]	50	1,033	590	0.57	11.8	25.5	7.54
	151[e]	0					25.5	
					P = 0.207[f]			
+ S9								
Summary: Negative								
Dimethylsulfoxide		50	1,047	531	0.50	10.6	25.8	
Cyclophosphamide[d]	0.35	50	1,048	723	0.68	14.5	25.8	36.03
	2	5	108	159	1.47	31.8	25.8	190.29
Ethylbenzene	125	50	1,044	561	0.53	11.2	25.8	5.95
	137.5	50	1,041	531	0.51	10.6	25.8	0.58
	150[e]	50	1,037	516	0.49	10.3	25.8	−1.89
	175[e]	0						
					P = 0.713			

[a] Study was performed at Litton Bionetics, Inc. A detailed description of the protocol is presented in Galloway *et al*. (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Precipitate on plate
[f] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Ethylbenzene[a]

-S9					+ S9				
Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 10.5 hours					Harvest time: 10.5 hours				
Summary: Negative					Summary: Negative				
Dimethylsulfoxide[b]					Dimethylsulfoxide				
	100	3	0.03	3		100	3	0.03	3
Mitomycin-C[c]					Cyclophosphamide[c]				
1	50	16	0.32	22	50	50	23	0.46	36
Ethylbenzene					Ethylbenzene				
75	100	1	0.01	1	75	100	4	0.04	4
100	100	3	0.03	3	100	100	1	0.01	1
125	100	5	0.05	5	125	100	1	0.01	1
150	0				150	0			
				P = 0.150[d]					P = 0.917

[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented in Galloway *et al*. (1987). Abs = aberrations
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE E5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Ethylbenzene by Inhalation for 13 Weeks[a]

Compound	Dose (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated Cells/1,000 Cells[b] PCEs	Micronucleated Cells/1,000 Cells[b] NCEs	PCEs[b] (%)
Male					
	0	8	2.18 ± 0.56	1.54 ± 0.16	2.22 ± 0.10
	500	10	2.04 ± 0.31	1.68 ± 0.13	3.13 ± 0.94
	750	9	1.90 ± 0.53	1.90 ± 0.13	1.97 ± 0.09
	1,000	10	1.21 ± 0.20	1.59 ± 0.16	2.02 ± 0.14
Trend test[c]			P = 0.928	P = 0.816	
ANOVA[d]					P = 0.278
Female					
	0	10	1.54 ± 0.56	0.92 ± 0.11	1.74 ± 0.14
	500	10	2.64 ± 0.53	1.01 ± 0.12	1.83 ± 0.18
	750	10	1.87 ± 0.38	1.32 ± 0.22	1.85 ± 0.15
	1,000	10	1.01 ± 0.26	1.12 ± 0.12	1.80 ± 0.15
Trend test			P = 0.817	P = 0.077	
ANOVA					P = 0.886
Overall trend			P = 0.951	P = 0.149	
Overall ANOVA					P = 0.684

[a] Study was performed at the USDA Western Regional Center. The protocol is presented in MacGregor *et al*. (1990). PCE = polychromatic erythrocyte; NCE = normochromatic erythrocyte. At least 2,000 PCEs and 10,000 NCEs were scored from each animal.
[b] Mean ± standard error
[c] Cochran-Armitage linear regression of proportions for PCEs or linear contrasts from analysis of variance for NCEs
[d] Analysis of variance on ranks

APPENDIX F
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF ETHYLBENZENE

Ethylbenzene was obtained from ARCO Chemical Company (Newtown Square, PA) in two lots (A060989 and A051890) that were used during the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the ethylbenzene studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless, pungent smelling, volatile liquid, was identified as ethylbenzene by infrared, ultraviolet/visible (lot A060989 only), and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) of ethylbenzene. The infrared and nuclear magnetic resonance spectra are presented in Figures F1 and F2. The boiling point and density of the chemical were also consistent with literature references (*Merck Index*, 1983).

The purity of lot A060989 was determined by elemental analyses, Karl Fischer water analysis, peroxide determination, and gas chromatography. To determine peroxide concentrations, a sample of ethylbenzene was refluxed with isopropyl alcohol, glacial acetic acid, and sodium iodide; liberated iodine was titrated with 0.1 N sodium thiosulfate to the starch endpoint. Gas chromatography was performed using a flame ionization detector. Two systems were used:

A) 1% SP-1000 on 80/100 Supelcoport glass column, with a nitrogen carrier gas at a flow rate of 70 mL/minute, and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

B) DB-5 Megabore capillary fused-silica column with a helium carrier gas at a flow rate of 10 mL/minute, a makeup gas of nitrogen at a flow rate of 20 mL/minute, and an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for ethylbenzene. Karl Fischer water analysis indicated less than 0.05% water. Iodometric titration revealed no peroxide. Gas chromatography by each system revealed a major peak and no impurities with areas greater than 0.1% relative to the major peak. Major peak comparisons of lot A060989 with a previously analyzed lot of ethylbenzene (lot K061786) not used in the current studies indicated a purity of 101.0% ± 0.5% for lot A060989 relative to lot K061786. The overall purity of lot A060989 was determined to be greater than 99%.

Additional analyses of lot A060989 were performed with gas chromatography/mass spectrometry to identify and quantify cumene in the bulk ethylbenzene. The gas chromatograph system included a DB-5 fused-silica capillary column with a helium carrier gas at a linear flow rate of 30 cm^3/second and an oven temperature program of 60° C for 5 minutes, then 60° to 200° C at 10° C per minute; injection was performed with a 30-second splitless delay. Tridecane was added as an internal standard to the cumene standard solution. Cumene was identified by comparison of retention times and specific ion ratios to the cumene standard. Cumene in lot A060989 had a retention time of 5.8 minutes and a specific ion ratio of 19:100:23, compared to a retention time of 5.6 minutes and an ion ratio of 20:100:24 for the standard. System B described for purity analyses, with cumene added as a standard, was used to quantify cumene; 62 ± 3.1 ppm was detected.

The purity of lot A051890 was determined by iodometric titration for peroxide and by gas chromatography with system A, but with a 10% SP-1000 on 80/100 Supelcoport glass column. Less than 2 ppm peroxide was detected. Gas chromatography indicated one impurity with an area of 0.1% relative to the major peak. The overall purity of lot A051890 was determined to be greater than 99%.

Accelerated stability studies of lot K061786 were performed by the analytical chemistry laboratory. Gas chromatography was performed with system A but with a 10% SP-1000 column and 87° C isothermal temperature. These studies indicated that ethylbenzene is stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature in the original steel containers until just prior to use, when it was transferred to amber glass bottles with Teflon®-lined caps and a nitrogen headspace. The rapid use and small shipment sizes of ethylbenzene made stability monitoring unnecessary during the studies; however, the peroxide content of the bulk chemical was tested monthly with iodometric titration. The concentration of peroxide ranged from 1.12 to 10.7 ppm.

VAPOR GENERATION AND EXPOSURE SYSTEM

A diagram of the ethylbenzene generation and delivery system is shown in Figure F3. Ethylbenzene vapor was produced by flash evaporator units. Liquid ethylbenzene was pumped by fine metering pumps from a reservoir into the top of a 30-cm-long, 20-mm internal diameter, Hempel distillation column packed with 3-mm diameter glass beads. At its lower end, the column was fitted into a two-armed 500-mL glass flask. One arm of the flask allowed access by a thermocouple that, in conjunction with a thermostated heating tape, maintained the column temperature at 150° ± 15° C. Nitrogen carrier gas at 95 psi was bled from a high-pressure liquid nitrogen tank monitored by a weight scale, was passed through a manifold, and entered the flask through the second arm; it was heated to 200° ± 50° C by a mantle surrounding the flask. The nitrogen gas carried ethylbenzene vapor into stainless steel transfer lines heated to 75° C by a heating tape. Magnehelic gauges were installed in the carrier gas lines immediately before the flash evaporators to monitor for blockages; pressure alarms ensured that the nitrogen gas pressure remained within the appropriate range. Transfer lines led to exposure chambers. Each exposure chamber was supplied by a separate flash evaporator unit.

Exposure concentrations for individual exposure chambers were created by varying the ethylbenzene flow rate to the individual flash evaporation units. Ethylbenzene vapor concentrations of 75, 250, and 750 ppm were created by ethylbenzene flow rates of 0.19, 0.63, and 1.9 mL/minute. To prevent saturation of the vapor streams, nitrogen flow rates were maintained at 5 L/minute for 75 and 250 ppm chambers and 10 L/minute for 750 ppm chambers. Each carrier gas line was fitted with a pressure release valve to shield the glass flash evaporator from pressure buildup due to blockage. At the chamber inlets, the ethylbenzene vapor passed through venturi-type plenums to enhance complete mixing with HEPA- and charcoal-filtered air.

Stainless-steel chambers (Hazleton H-2000®) manufactured by Lab Products, Inc. (Maywood, NJ) were used throughout the studies. A diagram of the inhalation suite is shown in Figure F4. The total volume of each chamber was 2.3 m^3; the active mixing volume of each chamber was 1.7 m^3. The chamber was designed so that uniform vapor concentrations could be maintained throughout the chamber when catch pans were in place.

The 750 ppm chambers were sampled once during the first full week of exposure for the presence of aerosol by a Quartz Crystal Microbalance Cascade Impactor (California Measurements, Sierra Madre, CA). Aerosol concentrations prior to and during exposure were 0.1492 ± 0.0121 mg/m^3 and 0.0904 ± 0.0270 mg/m^3, respectively, for rats and 0.1772 ± 0.0633 mg/m^3 and 0.2522 ± 0.0605 mg/m^3,

respectively, for mice. These results indicate that aerosol formation due to test atmosphere generation was not significant.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of ethylbenzene were monitored automatically by an on-line gas chromatograph (Hewlett Packard Model 5880A; Hewlett Packard, Palo Alto, CA) with a flame ionization detector and a 10% SP-1000 on 80/100 Supelcoport glass column. Samples were drawn from supply lines leading to exposure chambers and the control chamber at least once every hour by a six-port gas sample valve in conjunction with a 10-port stream selector valve. A similarly equipped gas chromatograph was used as a backup and for the analysis of grab samples.

The on-line monitoring system was calibrated using certified gas standards prepared by Scott Specialty Gases (Troy, MI) and Air Products Specialty Gases (Chicago, IL). Calibration was then verified by analyzing liquid standards prepared gravimetrically with bulk ethylbenzene. Calibrations were performed prior to the beginning of the studies, weekly for the first 2 weeks of the studies, and monthly thereafter using the certified gas standards. Daily calibration checks were performed by analyzing a randomly selected standard gas sample; if the concentration deviated by more than 10% from the current calibration curve, a full-range recalibration was performed at the earliest convenient time.

Monthly calibrations of the backup gas chromatograph used in these studies were performed by collecting samples of the gas standards in gas-tight syringes and injecting them into the gas chromatograph. Daily calibration checks were performed by analyzing randomly selected standard gas samples; if the concentration deviated by more than 10% from the current calibration curve, a full range recalibration was performed. Summaries of the chamber concentrations are presented in Table F1.

CHAMBER ATMOSPHERE CHARACTERIZATION

The times for the exposure concentration to build up to 90% of the final exposure concentration (T_{90}) and to decay to 10% of the exposure concentration (T_{10}) were measured in the 750 ppm exposure chambers with animals present during the first 2 weeks of the studies. At a chamber airflow rate of 15 air changes per hour, the theoretical value for both T_{90} and T_{10} is 10 minutes. Plots of time-concentration histories during the first 2 weeks of the studies indicated T_{90} and T_{10} values of 15 minutes; therefore, 15 minutes was used for the T_{90} value throughout the studies. Actual T_{90} values ranged from 11.4 to 15 minutes for rats and from 8.9 to 12.3 minutes for mice. Actual T_{10} values ranged from 10.5 to 11.7 minutes for rats and from 9.9 to 10.7 minutes for mice.

Inhalation chambers were sampled to determine the uniformity of ethylbenzene concentrations; grab samples from 12 shelf positions within the exposure chamber were analyzed by an off-line gas chromatograph. Grab samples were collected in gas-tight syringes from sampling ports in the exposure chambers without animals present before exposures began and with animals present approximately every 90 days during the studies. Chamber concentration uniformity was maintained throughout the studies.

The persistence of ethylbenzene following exposure was monitored by gas chromatography in the 750 ppm chambers without animals present, at 4-minute intervals for at least 2 hours, and with animals present once per hour for at least 2 hours during the first week of the studies and at 90-day intervals afterward. No ethylbenzene was detectable after 2 hours (detection limit 0.44 ppm).

The stability of ethylbenzene was monitored in the generator reservoirs of the 75 and 750 ppm chambers. Samples were collected without animals in the chambers, before the studies began, over a 3-day simulated

exposure period; samples were collected at the beginning of the first day and after 6 hours of ethylbenzene generation on the third day. Samples were also collected on day 1 of the studies, during the first hour of exposure, and on day 5, during the sixth hour of exposure. Grab samples (1 mL) were diluted to 100 mL with methylene chloride and analyzed by gas chromatography. No contaminants or degradation products with peak areas of 0.1% or greater relative to the major peak were found in any of the generator reservoir samples.

Grab samples from occupied and unoccupied 75 and 750 ppm chambers were analyzed for degradation products. Grab samples (10 mL) of chamber atmospheres were collected in gas-tight syringes and analyzed by gas chromatography. Samples were collected without animals in the chambers, before the studies began, over a 3-day simulated exposure period; samples were collected at the beginning of the first day and after 6 hours of ethylbenzene generation on the third day. Sampling was also performed every 90 days throughout the study; samples were collected during the first hour of the first day of the exposure week and during the sixth hour of day 5 of the exposure week. One small impurity with an area less than 0.04% of the ethylbenzene peak area was detected in samples taken from the 750 ppm chambers.

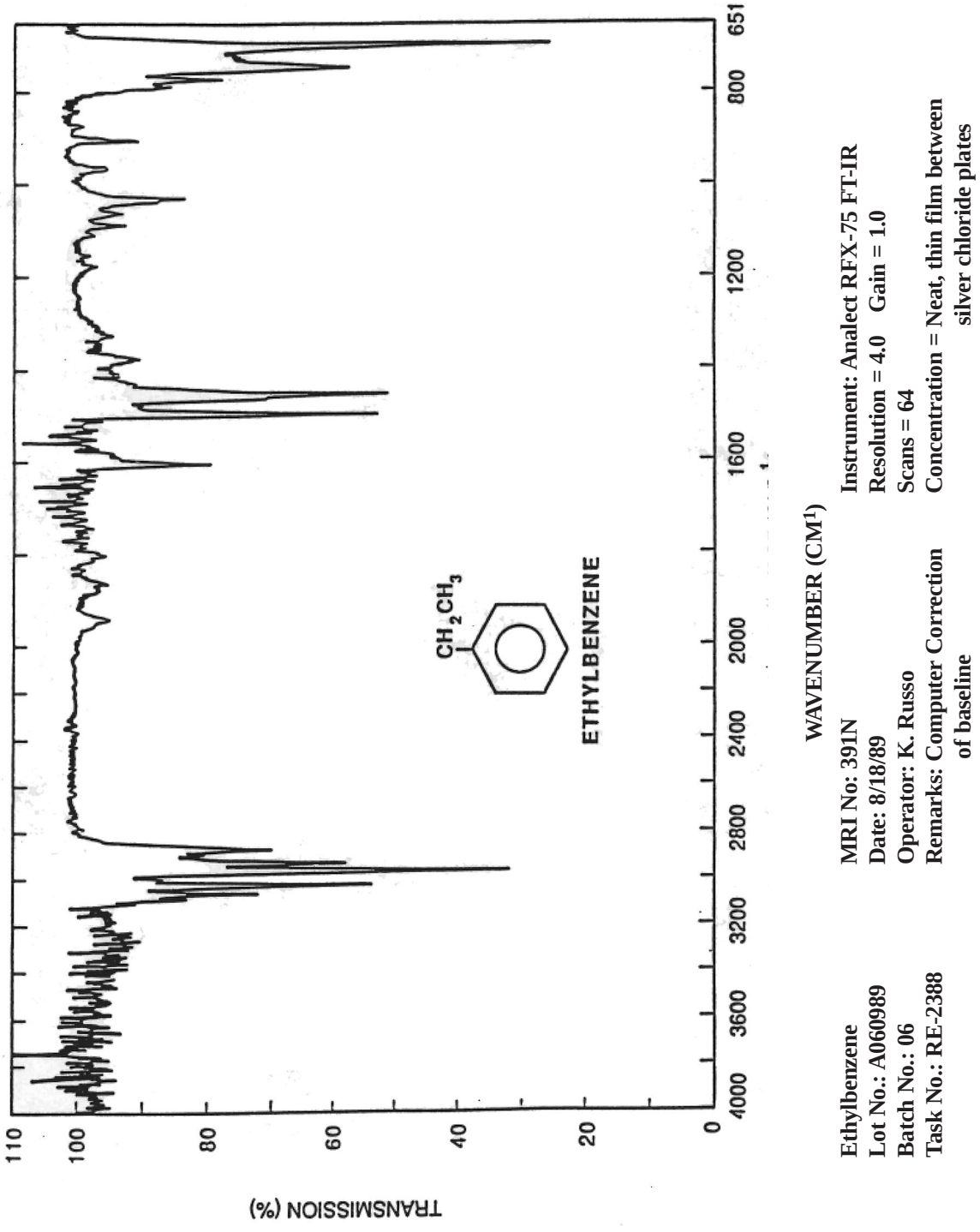

FIGURE F1
Infrared Absorption Spectrum of Ethylbenzene

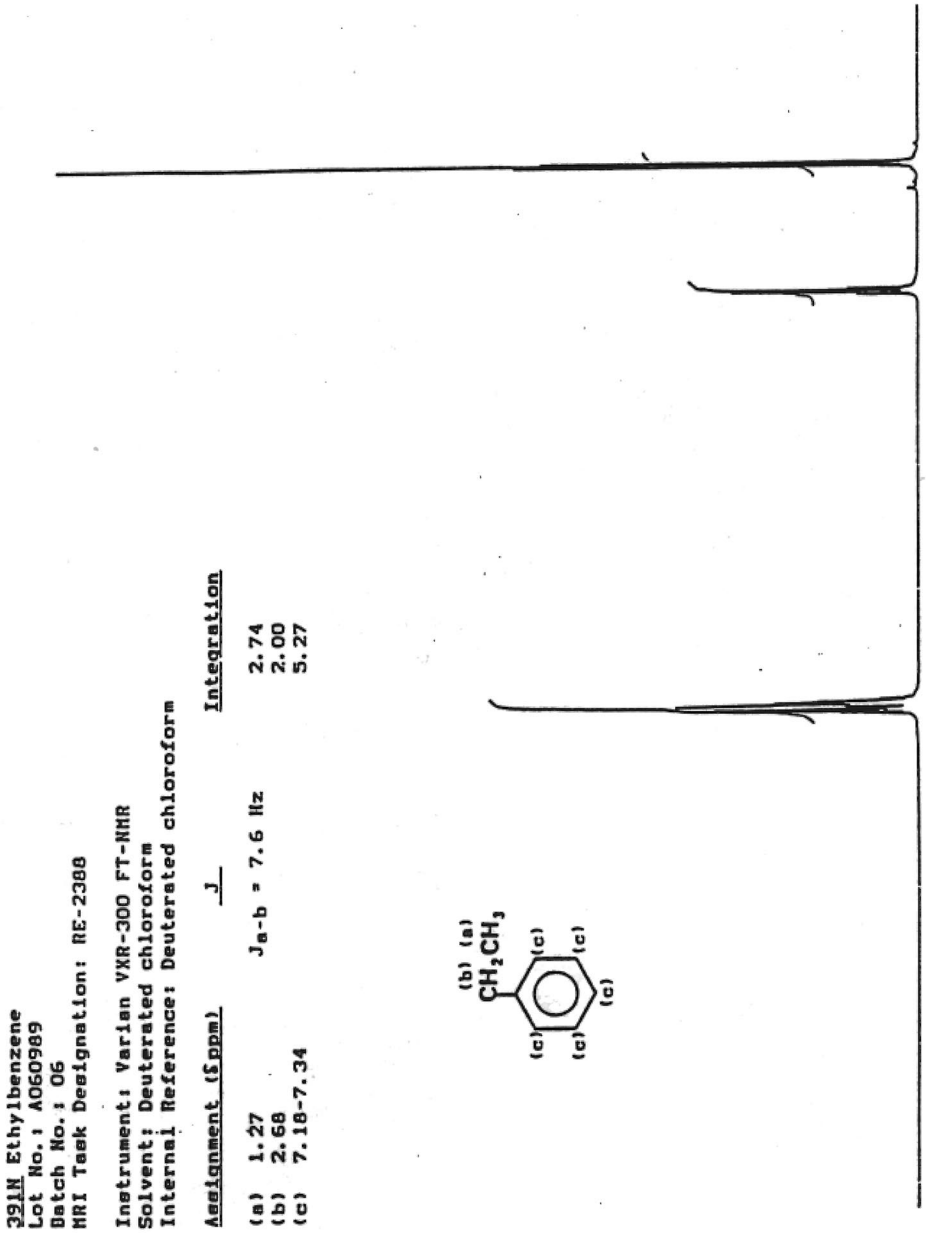

FIGURE F2
Nuclear Magnetic Resonance Spectrum of Ethylbenzene

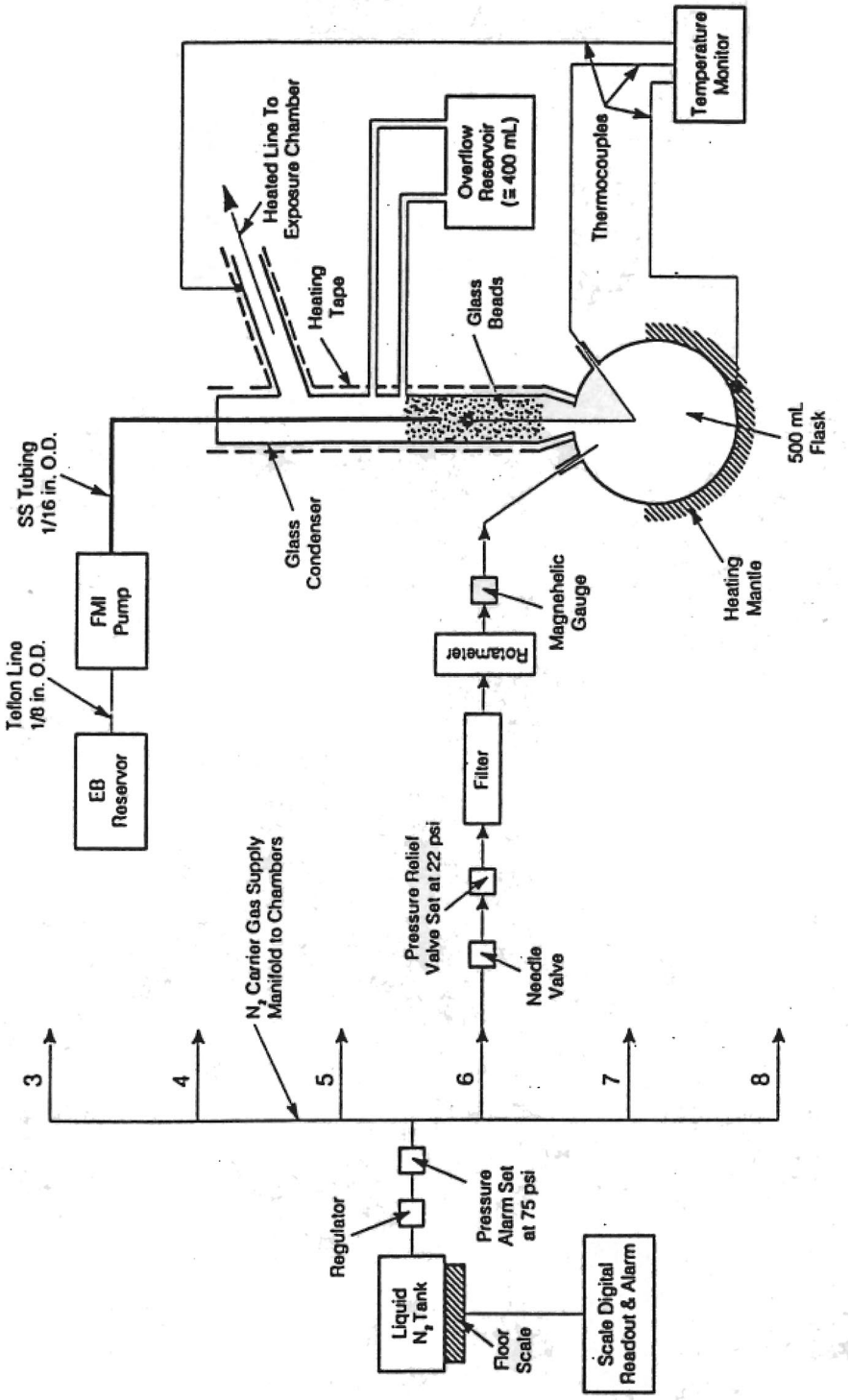

FIGURE F3
Schematic of Generation and Delivery System

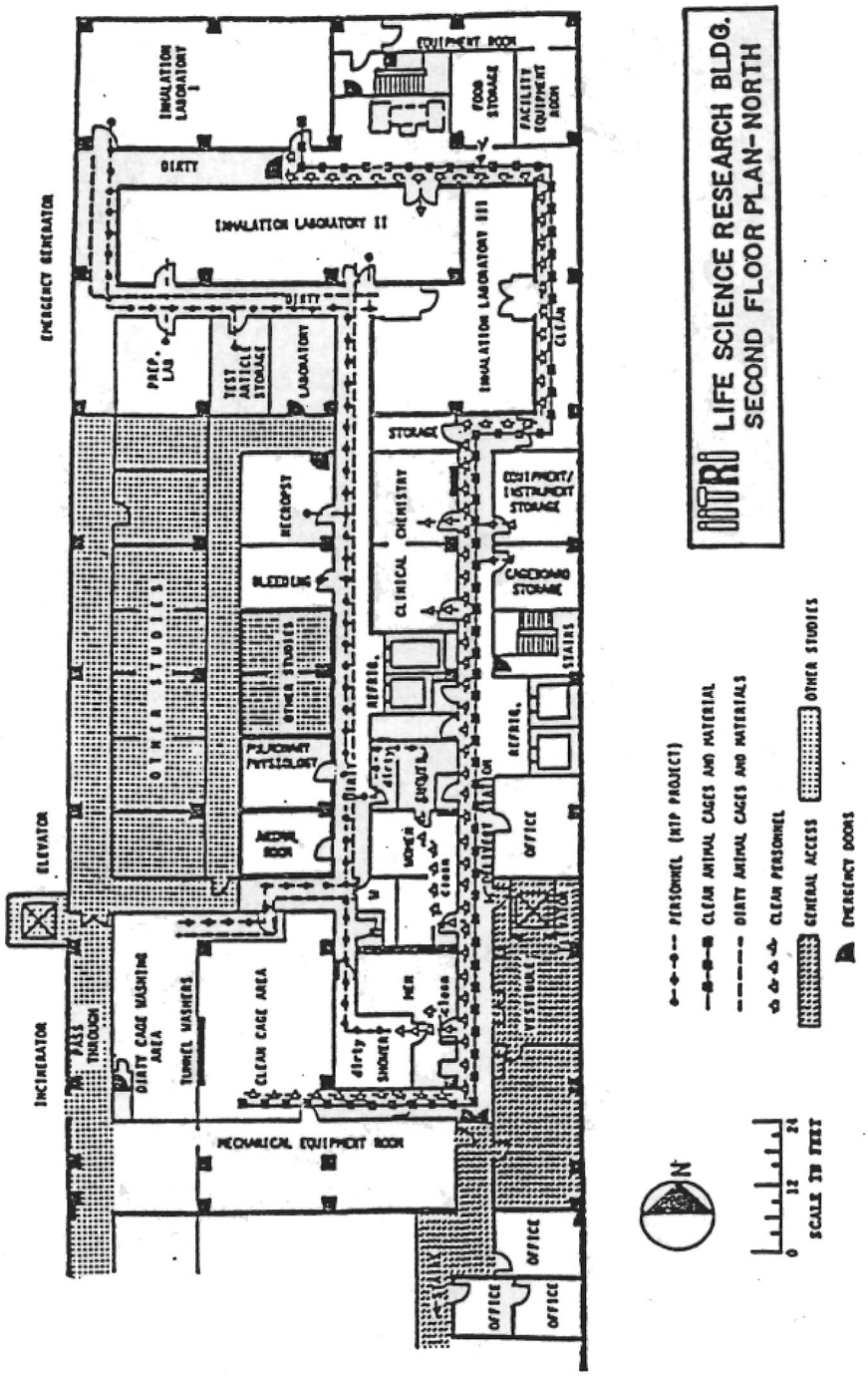

FIGURE F4
Inhalation Suite

TABLE F1
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Ethylbenzene

Target Concentration (ppm)	Total Number of Readings[a]	Average Concentration[b] (ppm)
Rat Chambers		
75	104	74.8 ± 1.7
250	104	250 ± 4
750	104	749 ± 7
Mouse Chambers		
75	103	75.2 ± 1.5
250	103	248 ± 5
750	103	748 ± 9

[a] Number of weekly means
[b] Mean ± standard deviation; average of weekly means

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

TABLE G1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE G2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE G3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.42 ± 0.56	22.2 — 24.3	25
Crude fat (% by weight)	5.30 ± 0.16	5.00 — 5.60	25
Crude fiber (% by weight)	3.49 ± 0.41	2.60 — 4.30	25
Ash (% by weight)	6.37 ± 0.18	6.11 — 6.81	25
Amino Acids (% total diet)			
Arginine	1.280 ± 0.083	1.110 — 1.390	11
Cystine	0.308 ± 0.071	0.181 — 0.400	11
Glycine	1.158 ± 0.048	1.060 — 1.220	11
Histidine	0.584 ± 0.027	0.531 — 0.630	11
Isoleucine	0.917 ± 0.033	0.867 — 0.965	11
Leucine	1.975 ± 0.051	1.850 — 2.040	11
Lysine	1.274 ± 0.049	1.200 — 1.370	11
Methionine	0.437 ± 0.109	0.306 — 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 — 1.110	11
Threonine	0.904 ± 0.058	0.824 — 0.985	11
Tryptophan	0.218 ± 0.153	0.107 — 0.671	11
Tyrosine	0.685 ± 0.094	0.564 — 0.794	11
Valine	1.086 ± 0.055	0.962 — 1.170	11
Essential Fatty Acids			
Linoleic	2.407 ± 0.227	1.830 — 2.570	10
Linolenic	0.259 ± 0.065	0.100 — 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,595 ± 1,548	4,180 — 11,450	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 — 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 — 48.9	11
Thiamine (ppm)	18.16 ± 1.54	15.0 — 21.0	25
Riboflavin (ppm)	7.83 ± 0.923	6.10 — 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0 — 150.0	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 — 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 — 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 — 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 — 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 — 65.0	11
Choline (ppm)	2,991 ± 382	2,300 — 3,430	10
Minerals			
Calcium (%)	1.17 ± 0.10	1.00 — 1.49	25
Phosphorus (%)	0.93 ± 0.03	0.850 — 1.00	25
Potassium (%)	0.886 ± 0.063	0.772 — 0.971	9
Chloride(%)	0.529 ± 0.087	0.380 — 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 — 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 — 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 — 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 — 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 — 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 — 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 — 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 — 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 — 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 — 1.15	7

TABLE G4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.37 ± 0.18	0.10 — 0.70	25
Cadmium (ppm)	0.10 ± 0.07	0.05 — 0.20	25
Lead (ppm)	0.30 ± 0.23	0.10 — 1.00	25
Mercury (ppm)[c]	0.02	0.02 — 0.03	25
Selenium (ppm)	0.33 ± 0.12	0.05 — 0.60	25
Aflatoxins (ppm)	< 5.0		25
Nitrate nitrogen (ppm)[d]	11.72 ± 5.20	2.90 — 21.0	25
Nitrite nitrogen (ppm)[d]	0.23 ± 0.18	0.10 — 0.70	25
BHA (ppm)[e]	1.88 ± 1.94	1.00 — 10.0	25
BHT (ppm)[e]	1.56 ± 1.58	1.0 — 8.00	25
Aerobic plate count (CFU/g)	78,748 ± 143,028	4,100 — 710,000	25
Coliform (MPN/g)	3 ± 0.2	3 — 4	25
Escherichia coli (MPN/g)	< 3		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[f]	7.25 ± 1.71	4.80 — 11.40	25
N-Nitrosodimethylamine (ppb)[f]	5.50 ± 1.30	3.80 — 9.10	25
N-Nitrosopyrrolidine (ppb)[f]	1.75 ± 1.00	1.00 — 4.30	25
Pesticides (ppm)			
α-BHC	< 0.01		25
β-BHC	< 0.02		25
γ-BHC	< 0.01		25
δ-BHC	< 0.01		25
Heptachlor	< 0.01		25
Aldrin	< 0.01		25
Heptachlor epoxide	< 0.01		25
DDE	< 0.01		25
DDD	< 0.01		25
DDT	< 0.01		25
HCB	< 0.01		25
Mirex	< 0.01		25
Methoxychlor	< 0.05		25
Dieldrin	< 0.01		25
Endrin	< 0.01		25
Telodrin	< 0.01		25
Chlordane	< 0.05		25
Toxaphene	< 0.10		25
Estimated PCBs	< 0.20		25
Ronnel	< 0.01		25
Ethion	< 0.02		25
Trithion	< 0.05		25
Diazinon	< 0.10		25
Methyl parathion	< 0.02		25
Ethyl parathion	< 0.02		25
Malathion	0.24 ± 0.21	0.05 — 0.97	25
Endosulfan I	< 0.01		25
Endosulfan II	< 0.01		25
Endosulfan sulfate	< 0.03		25

[a] CFU = colony-forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All but three values were less than the detection limit; the detection limit was used for the low end of the range.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX H
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which the blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination
MICE	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	6 and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE (continued)	
Immunofluorescence Assay	
EDIM	6 and 12 months, study termination
GDVII	12 months
MHV	6 and 12 months
Mouse adenoma virus-FL	Study termination
Reovirus 3	6 and 12 months
Sendai	6 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table H1.

TABLE H1
Murine Virus Antibody Determinations for Rats and Mice in the 2-Year Inhalation Studies of Ethylbenzene

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
Rats		
6 Months	0/24	None positive
12 Months	0/24	None positive
18 Months	0/22	None positive
Study termination	1/10	*Mycoplasma arthritidis*[a]
Mice		
6 Months	0/10	None positive
12 Months	1/9	Reovirus 3
18 Months	0/8	None positive
Study termination	0/10	None positive

[a] Further evaluation of the sample positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only one sample was positive, and there were no clinical findings or histopathologic changes of *M. athritidis* infection in the rat with the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered to be a false positive.