NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 327

TOXICOLOGY AND CARCINOGENESIS STUDIES OF XYLENES (MIXED)

(60% *m*-XYLENE, 14% *p*-XYLENE, 9% *o*-XYLENE, and 17% ETHYLBENZENE)

(CAS NO. 1330-20-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

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(GAVAGE STUDIES)

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

December 1986

NTP TR 327

NIH Publication No. 87-2583

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

NOTE TO THE READER

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

Five categories of interpretative conclusions were adopted in June 1983 for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

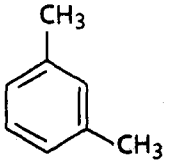
Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

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

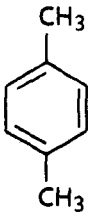
This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and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

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

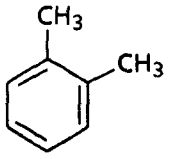
These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public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



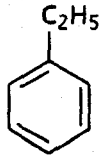
m-Xylene
(60%)



p-Xylene
(14%)



o-Xylene
(9%)



Ethylbenzene
(17%)

XYLENES (MIXED)

CAS No. 1330-20-7

C_8H_{10} Molecular weight 106.2

ABSTRACT

The technical grade of xylenes (mixed) (hereafter termed xylenes) contains the three isomeric forms and ethylbenzene (percentage composition shown above). The annual production for 1985 was approximately 7.4×10^8 gallons. Xylenes is used as a solvent and a cleaning agent and as a degreaser and is a constituent of aviation and automobile fuels. Xylenes is also used in the production of benzoic acid, phthalic anhydride, and isophthalic and terephthalic acids as well as their dimethyl esters.

Toxicology and carcinogenesis studies of xylenes were conducted in laboratory animals because a large number of workers are exposed and because the long-term effects of exposure to xylenes were not known. Exposure for the present studies was by gavage in corn oil. In single-administration studies, groups of five F344/N rats and B6C3F$_1$ mice of each sex received 500, 1,000, 2,000, 4,000, or 6,000 mg/kg. Administration of xylenes caused deaths at 6,000 mg/kg in rats and mice of each sex and at 4,000 mg/kg in male rats. In rats, clinical signs observed within 24 hours of dosing at 4,000 mg/kg included prostration, muscular incoordination, and loss of hind limb movement; these effects continued through the second week of observation. Tremors, prone position, and slowed breathing were recorded for mice on day 3, but all mice appeared normal by the end of the 2-week observation period. In 14-day studies, groups of five rats of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg, and groups of five mice of each sex received 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg. Chemical-related mortality occurred only at 2,000 mg/kg in rats and at 4,000 mg/kg in mice. Rats and mice exhibited shallow breathing and prostration within 48 hours following dosing at 2,000 mg/kg. These signs persisted until day 12 for rats, but no clinical signs were noted during the second week for mice. In 13-week studies, groups of 10 rats of each sex received 0, 62.5, 125, 250, 500, or 1,000 mg/kg, and groups of 10 mice of each sex received 0, 125, 250, 500, 1,000, or 2,000 mg/kg. No deaths or clinical signs of toxicity were recorded in rats. However, high dose male rats gained 15% less weight and females 8% less weight than did the vehicle controls. Two female mice died at the 2,000 mg/kg dose. Lethargy, short and shallow breathing, unsteadiness, tremors, and paresis were observed for both sexes in the 2,000 mg/kg group within 5-10 minutes after dosing and lasted for 15-60 minutes.

Two-year toxicology and carcinogenesis studies were conducted by administering 0, 250, or 500 mg/kg xylenes in corn oil by gavage to groups of 50 F344/N rats of each sex, 5 days per week for 103 weeks.

Groups of 50 B6C3F$_1$ mice of each sex were administered 0, 500, or 1,000 mg/kg xylenes on the same schedule. Although the mortality was dose related in male rats (final survival: vehicle control, 36/50; low dose, 26/50; high dose, 20/50), many of the early deaths in the dosed males were gavage related. Body weights of the high dose male rats were 5%-8% lower than those of the vehicle controls after week 59. The mean body weights of low dose and vehicle control male rats and those of dosed and vehicle control female rats were comparable. Survival rates of female rats and both sexes of dosed mice were not significantly different from those of the vehicle controls. The mean weights of dosed male and female mice were comparable to those of the vehicle controls. Hyperactivity lasting 5-30 minutes was observed in high dose mice after dosing, beginning after week 4 and continuing through week 103.

At no site was the incidence of nonneoplastic or neoplastic lesions in dosed rats or mice of either sex considered to be related to the administration of xylenes.

Neither xylenes nor any of its components (*o*-xylene, *m*-xylene, *p*-xylene, or ethylbenzene) were mutagenic when tested with or without metabolic activation in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98 with the preincubation protocol. In addition, ethylbenzene was tested in cytogenetic assays using cultured Chinese hamster ovary cells both with and without metabolic activation; neither sister-chromatid exchanges nor chromosomal aberrations were induced by ethylbenzene.

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

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of xylenes (mixed) for male or female F344/N rats given 250 or 500 mg/kg or for male or female B6C3F$_1$ mice given 500 or 1,000 mg/kg.

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*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

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APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on xylenes (mixed) on March 26, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF XYLENES (MIXED)

On March 26, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of xylenes (mixed) received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. W. Eastin, Jr., NTP, introduced the toxicology and carcinogenesis studies of xylenes (mixed) by reviewing the experimental designs, results, and proposed conclusions (no evidence of carcinogenicity in rats or mice).

Dr. Popp, a principal reviewer, agreed with the conclusions as written. He asked that a rationale be given for using the gavage route of exposure and that the most common or important route of human exposure be noted. [See page 20.]

As a second principal reviewer, Dr. Mirer agreed with the conclusions. He expressed concern that higher doses could have been given and thus a maximum tolerated dose was not achieved for female rats and male and female mice, even though the choice of dose was well justified. Dr. Eastin indicated that the doses were appropriate based on the results of the 13-week studies and that the marginally lower body weights in male rats gave some indication that higher doses might not be tolerated.

As a third principal reviewer, Dr. Chinchilli also agreed with the conclusions. He asked that the randomization scheme and the process for animal cage rotation be described in the Materials and Methods section. Dr. Eastin said that cages were not being rotated at the time of these studies, although cage rotation is practiced with more recent studies. Dr. J. Huff, NTP, stated that this information would be added to the Materials and Methods section in all Technical Reports [page 30].

Dr. Mirer moved that the Technical Report on xylenes (mixed) be accepted with the conclusions as written for rats and mice of each sex, no evidence of carcinogenicity. Dr. Popp seconded the motion, and it was approved by 10 affirmative votes with 1 abstention (Dr. Scala).

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Xylenes (Mixed) is based on 13-week studies that began in August 1979 and ended in November 1979 and on the 2-year studies that began in July 1980 and ended in July 1982 at Battelle Columbus Laboratories.

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I. INTRODUCTION

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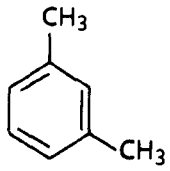
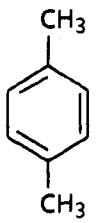
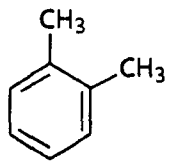


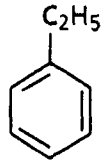
m-Xylene
(60%)



p-Xylene
(14%)



o-Xylene
(9%)



Ethylbenzene
(17%)

XYLENES (MIXED)

CAS No. 1330-20-7

C_8H_{10} Molecular weight 106.2

Production, Physical Properties, and Uses

The technical grade of xylenes (mixed) (also referred to as xylenes in this report) is a mixture of all three isomers (*m*-xylene predominating) and ethylbenzene and may also contain small amounts of toluene, trimethylbenzene, phenol, thiophene, pyridine, and nonaromatic hydrocarbons (Sittig, 1985). The exact proportion of commercial xylenes constituents is somewhat variable and depends on the material from which it is produced. Xylenes is produced primarily from petroleum; smaller amounts are produced from coal tar (NIOSH, 1975). The NTP studies used xylenes produced from petroleum with less than 0.3% volatile impurities (percentage composition of each major constituent is shown above).

Xylenes is a clear, colorless, aromatic liquid with a melting point of less than −50° C, a boiling point of 137°-140° C, a specific gravity of 0.86-0.88 at 20°/4° C, and a vapor pressure of approximately 10 mm Hg at 28° C. Xylenes is insoluble in water and very soluble in ethyl alcohol and ethyl ether (CRC, 1982-1983; Merck Index, 1983).

Xylenes is used as a solvent in the paint, printing, rubber, and leather industries and in the manufacture of mirrors. The mixture is also used as a cleaning agent (especially in microscope technique), as a degreaser, and as a constituent of aviation and automobile fuels (Browning, 1965; Ikeda et al., 1984). Xylenes is a raw material for the production of benzoic acid, phthalic anhydride, and isophthalic and terephthalic acids, as well as their dimethyl esters (used in the manufacture of polyester fibers, dyes, and other organics) (Merck Index, 1983). The total production of *o*- and *p*-xylenes in 1984 was 2.2×10^{12} g/year (6.8×10^{8} gallons) (USITC, 1985). In 1984, xylene was listed 22nd among the top commercial products ranked by production volume (Chem. Eng. News, 1985).

Occupational Exposure

Approximately 140,000 workers are potentially exposed to xylenes in the United States (NIOSH, 1975). The most frequent routes of occupational exposure for xylenes are inhalation and dermal (Sittig, 1985). In a survey done to obtain information about contaminants for which the Environmental Protection Agency is considering the development of drinking water criteria, xylenes was identified as a contaminant of ground water in the vicinity of hazardous waste disposal sites (Lockheed Engineering and Management Services Co., Inc., 1985). In these areas, there is increased potential for exposure to xylenes in the drinking water.

The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA)

recommend that the occupational air concentration of xylenes not exceed 100 ppm, determined as a time-weighted-average (TWA) exposure for up to a 10-hour workday, 40-hour workweek, with a ceiling concentration of 200 ppm as determined in a 10-minute sampling period (NIOSH, 1975; OSHA, 1975).

Several reviews of the literature on xylene including toxicity studies have been published (NIOSH, 1975; Miller et al., 1976; Mazella et al., 1978). The following summarizes the conclusions regarding occupational exposure. The major routes of exposure in industry are inhalation and dermal. It appears that there is little difference between the toxicity of individual xylene isomers and xylenes (mixed). Xylenes can have a narcotic effect at relatively high levels. Liver damage and kidney damage have been reported after inhalation of xylenes and liver damage after accidental ingestion. In all these instances, exposure was sufficient to cause unconsciousness or illness, but all those involved recovered fully. No published evidence of irreversible liver or kidney damage has been found. Liver necrosis and diffuse nephritis have been reported in rats that received intraperitoneal injections of xylenes. Early studies concluded that xylenes was myelotoxic. However, in all reported occupational exposures to xylenes, concomitant benzene exposure was either known or suspected. Findings of more recent animal studies in which exposure to xylenes did not produce significant hematologic changes were taken as evidence that xylenes is not myelotoxic. NIOSH (1975) concluded that a xylenes standard should protect against the irritating and narcotizing properties of xylenes, the only well-documented effects. No studies were cited which presented evidence for the carcinogenicity of xylenes alone.

In October 1977, the Interagency Testing Committee (ITC), as required by section 4(e) of the Toxic Substances Control Act (TSCA), designated xylenes to be studied for potential mutagenic and teratogenic effects and for epidemiology (TSCA, 1977). In December 1982, the EPA responded to the ITC that it did not plan to initiate rulemaking under section 4 (a) because sufficient data are available to reasonably predict the potential for mutagenic and teratogenic effects (Fed. Reg., 1982).

Metabolism

Percutaneous absorption of *o*-xylene was estimated to be 0.058 µmol/hour per cm^2 for SD-JCL rats (Tsuruta, 1982), 1.82 µmol/hour per cm^2 for mouse skin (strain unspecified), and 1.13 µmol/hour per cm^2 for human skin (Engstrom et al., 1977). Neat (stock) xylenes applied to the clipped skin of guinea pigs reportedly caused increased vascular permeability and produced erythema after 1 minute of exposure; the effect was diminished after about 5 minutes (Steele and Wilhelm, 1966).

Absorption by inhalation has been well studied in humans. Six men exposed to an industrial xylene mixture at concentrations of 435 mg/m^3 (100 ppm) or 870 mg/m^3 (200 ppm) absorbed 60% of the amount of xylenes supplied to the lungs (Astrand et al., 1978). The concentration in alveolar air was relatively low throughout the entire exposure. The ratio between the concentration in arterial blood (milligrams per kilogram) and alveolar air (milligrams per liter) was 30-40:1 at rest or during exercise. In humans exposed at 100 or 200 ppm during rest or exercise, the amount of solvent taken up was closely related to the amount of body fat (Engstrom and Bjurstrom, 1978).

Elovaara et al. (1984) studied the metabolism and disposition of inhaled *m*-xylene and ethylbenzene in Wistar rats at *m*-xylene:ethylbenzene concentrations of 0:0, 75:25, 300:100, or 600:200 ppm. Exposure occurred 6 hours per day for 5 days. The ratio of *m*-xylene to ethylbenzene in fat was 3:1. *m*-Xylene metabolites were excreted twice as fast as ethylbenzene metabolites.

This relationship between uptake of xylenes and deposition in body fat is supported by animal studies in which male Sprague-Dawley rats exposed by inhalation to labeled xylenes at 45 ppm for 1-8 hours were found to have the largest concentration of xylenes and metabolites in subcutaneous fat (Carlsson, 1981), and at 250 ppm, metabolite concentrations in the cerebrum,

cerebellum, and muscles were about 40% of the arterial blood concentrations.

The major metabolic pathway of xylenes involves the cytochrome P-450-dependent monooxygenase system and appears to be related to the route of exposure (Savolainen et al., 1978; Heinonen et al., 1983; Pyykko, 1980; Toftgard and Nilsen, 1982; Toftgard et al., 1983; Elovaara et al., 1984; Engstrom et al., 1984). Oral administration studies of xylenes have shown that methylhippuric acid in rats (Ogata et al., 1970) and rabbits (Bray et al., 1949) is the primary excretory product; only small amounts of methylbenzyl alcohol and dimethylphenol are detected in the urine (Bakke and Schelilne, 1970). However, Elovaara et al. (1984) exposed male Wistar rats by inhalation to *m*-xylene at 300 or 600 ppm for 6 hours and reported 2,4-dimethylphenol (16%), and *m*-methylbenzyl alcohol (2%) as excretory products, in addition to *m*-methylhippuric acid (82%). Smith et al. (1982) using perfused isolated rabbit lung and liver showed that lung tissue is deficient in alcohol dehydrogenase and that under in vitro conditions the major metabolite of *p*-xylene is *p*-methylbenzyl alcohol. Lung tissue also produced 2,5-dimethylphenol, a derivative not formed by perfused liver. It has been reported that the highest alcohol dehydrogenase activity occurs in liver; the lung contains less than 5% of the activity measured in liver (Bosron and Li, 1980). Thus, the difference in the results of xylenes metabolism in rats may be related to the route of exposure, i.e., oral versus inhalation. Figure 1 depicts the major metabolic pathways proposed for xylenes (Lauwerys, 1975; Smith et al., 1982; Elovaara et al., 1984; Engstrom et al., 1984).

Methylbenzyl alcohol and dimethylphenol, however, have not been reported as major metabolites in inhalation studies with humans. When volunteers were exposed to a commercial xylene mixture at 200 mg/m^3 (46 ppm) or 400 mg/m^3 (92 ppm) for 8 hours, 64% of the xylene isomers was absorbed (Toftgard and Gustafsson, 1980). Only 5% of the absorbed dose was excreted unchanged in expired air, and excretion of unmetabolized in the urine was negligible. The main mxylenes etabolites (greater than 95%) were isomers of methylbenzoic acid, and these were excreted in the urine as methylhippuric acid (i.e., conjugated with glycine). Methylhippuric acid was also found in the urine of volunteers exposed to xylenes (Dworzanski and Debowski, 1981) and of painters occupationally exposed to xylenes (Engstrom et al., 1979). Engstrom et al. (1984) measured the urinary metabolites of humans exposed to ethylbenzene and *m*-xylene at 150 ppm separately and together. Mandelic and phenylglyoxylic acids were present after ethylbenzene exposure and *m*-methylhippuric acid after *m*-xylene exposure. Combined exposure resulted in a mutual inhibition of the metabolism of each compound.

Ingestion of ethanol (0.8 g/kg) before a 4-hour inhalation exposure to *m*-xylene at 6.0 or 11.5 mmol/m^3 (147 or 282 ppm) produced changes in xylene kinetics.

After ethanol ingestion, blood levels of xylenes rose 150%-200% and urinary methylhippuric acid excretion declined about 50%, suggesting that ethanol decreased the metabolic clearance of xylenes by about one-half during xylenes inhalation. This effect of ethanol was thought to be the result of ethanol-mediated inhibition of microsomal metabolism (Riihimaki et al., 1982). These results support those from animal studies in which Wistar rats were exposed to xylenes and ethanol simultaneously at 300 ppm for 15-18 weeks. The behavioral and biochemical changes were interpreted to indicate an interaction of these two solvents (H. Savolainen et al., 1979).

Physiologic Effects

No electrocardiographic changes were observed when male CFY rats received short-term exposures to xylenes at 0.05-0.4 ml/100 g by the subcutaneous, intraperitoneal, or intravenous routes, but exposure by inhalation at 6,000 mg/m^3 (1,400 ppm) produced respiratory paralysis, bradyarrhythmia, and asystole (Morvai et al., 1976). Administration for longer periods (up to 6 months) produced disorders in repolarization and arrhythmia.

Chinchilla rabbits exposed to xylenes at concentrations of 50 mg/m^3 (12 ppm) or 200 mg/m^3

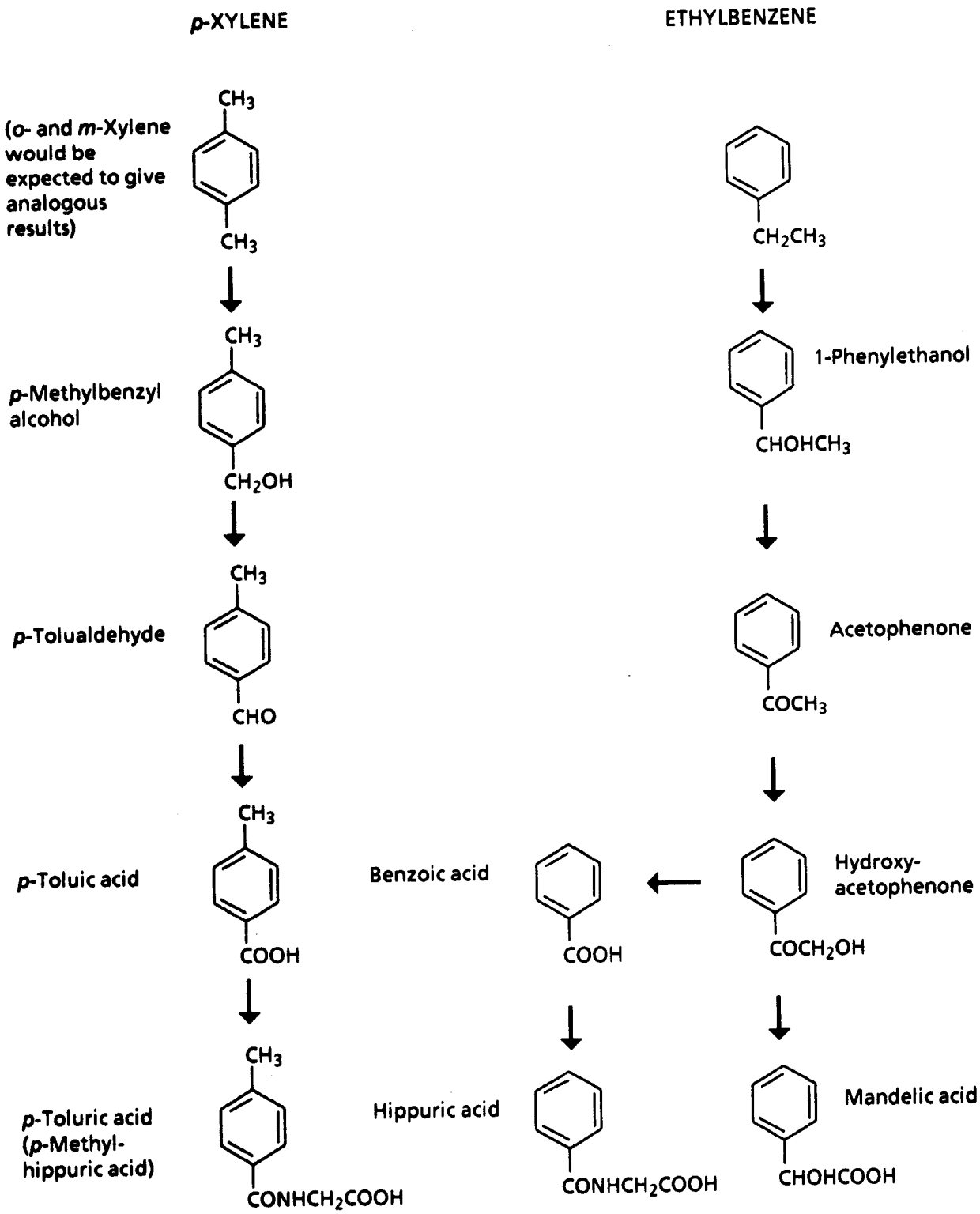


FIGURE 1. PROPOSED METABOLIC PATHWAYS OF XYLENES
(Lauwerys, 1975; Smith et al., 1982; Elovaara et al., 1984; Engstrom et al., 1984)

(46 ppm) had increased levels of hemoglobin, red blood cells, white blood cells, total protein, and urinary 17-ketosteroids and increased activity of the acetylcholine-mediating system. In these studies, the magnitude of maximum titers of agglutinin after immunization with typhoid vaccine and the duration of elevation of the titers served as indices of the state of immunobiologic reactivity. During the first 3 months, decreases in the immunobiologic reactivity and in body weights of exposed animals were noted, followed by normalization of these functions during months 4-8 and decompensation during months 9-12 (Kashin et al., 1968). Female Sprague-Dawley rats exposed by inhalation for 4 hours to *p*-xylene at 1,000, 1,500, or 2,000 ppm had increased levels of serum glutamic oxalic transaminase, serum glutamic pyruvic transaminase, glucose-6-phosphate dehydrogenase, isocitric dehydrogenase, lactic dehydrogenase, and 5'-nucleotidase 24 hours later (Patel et al., 1979). These changes are interpreted clinically to indicate hepatocellular damage.

Behavioral and Neuroendocrine Effects

In animal studies conducted by several investigators, xylenes affected behavior and was possibly neurotoxic. When male CFY rats were given intraperitoneal injections (volume unknown) of *m*-xylene diluted with sunflower oil (five dose levels, approximately 265-2,236 mg/kg) and then behavioral tests 30 minutes later, muscular weakness and disturbances in equilibrium were observed, but there were no signs of excitation (Paksy et al., 1982). However, Wistar rats exposed to xylenes at concentrations of 25 mg/liter (5,800 ppm) or 30 mg/liter (7,000 ppm), 5 hours per day for 7, 14, or 21 days exhibited excitation, hypersensitivity, and disorders of coordination and balance (Szuldrzynska, 1980). In addition, the animals limped, suggesting an effect of xylenes on the nervous system. Female Sprague-Dawley rats infused with 0.1%-10% xylenes intravenously for 60 minutes exhibited excitation of the vestibulo-oculomotor reflex (Tham et al., 1984). Several reports indicate neuroendocrine effects after xylene exposure. Xylenes administered by subcutaneous injection to rats at 0.5 g/kg per day or up to 30 days disrupted vascular permeability and caused hyperemia within the pituitary-hypothalamus system and a loss of neuron function (Bakhtizina and Sunargulov, 1976).

Adaptation of female rats (strain unspecified) to xylenes was accompanied by inhibition of ovary and pituitary functions (Berliner, 1977). The administration of estradiol or an ovariectomy disrupted the adaptation to the solvent. Exposure of male Sprague-Dawley rats to xylenes, *o*-xylene, *m*-xylene, *p*-xylene, or ethylbenzene at concentrations of 2,000 ppm (6 hours per day for 3 consecutive days) produced discrete increases of dopamine and noradrenaline levels in various parts of the hypothalamus and the median eminence 16-18 hours after the last exposure (Andersson et al., 1981). Only xylenes produced increased dopamine levels in the striatum and subcortical limbic forebrain.

There are fewer studies on the effects of xylenes on human behavior. When humans at rest or exercising were exposed for 70 minutes to xylenes or ethylbenzene at concentrations of 435 mg/m^3 (100 ppm) or 1,300 mg/m^3 (300 ppm), performance decrements in several central nervous system function tests were observed only in exercising subjects (Gamberale et al., 1978). When men were exposed to *m*-xylene at 100-200 ppm 6 hours per day for successive days and periodically at concentrations fluctuating from 100 to 400 ppm, adaptation with respect to equilibrium and reaction time occurred during subsequent exposure days, but effects were again discernible the following week (K. Savolainen et al., 1979). There was no dose-response relationship between eyes closed:eyes open ratio and blood xylenes concentration in humans exposed at 64-400 ppm (Savolainen and Riihimaki, 1981). The effects of xylenes in combination with alcohol have also been studied. Once a week for 9 consecutive weeks, men were administered 6 or 11.5 µmol/liter xylenes by inhalation either alone or after ingesting a single dose of 0.4 or 0.8 g/kg ethanol. Those administered xylenes alone did not show marked impairment of function on behavioral tests, whereas subjects administered ethanol alone did; ethanol and xylenes administered together produced additive effects (Savolainen, 1980). These results support similar findings observed in rats (H. Savolainen et al., 1979).

Toxicologic Effects

Carpenter et al. (1975) examined the effects of xylenes inhalation on rats, dogs, and cats. They reported an LT_{50} value of 90 minutes for rats that inhaled xylenes at 11,000 ppm, a concentration approaching air saturation. The LC_{50} value for rats was 6,700 ppm in a 4-hour exposure; cats succumbed within 2 hours at 9,500 ppm with apparent central nervous system effects. No significant effects occurred in beagle dogs or rats exposed to xylenes (6 hours per day, 5 days per week, for 13 weeks) at concentrations of 180, 460, or 810 ppm when compared with controls (Tatrai and Ungvary, 1980). Male CFY rats exposed at 3,500 ppm to *o*-xylene 8 hours per day for 6 weeks were reported to develop liver enlargement and to have lower weight gains than controls despite increased feed and fluid intake. A postmortem examination revealed no abnormalities.

Bowers et al. (1982) examined ultrastructural changes in the liver of young and aging male Long-Evans hooded rats exposed to methylated benzenes. Three-month-old rats were given 73 mg/kg *o*-xylene intraperitoneally for 3 days, and aging rats (12-19 months old) received 200 ppm in feed for 1, 2, 3, or 6 months. Young dosed rats had nodular liver lesions consisting of lipid droplets surrounded by macrophages and fibroblasts, but the hepatocytes were normal. Hepatocytes in aging rats developed vacuoles.

Nilsen and Toftgard (1980) studied the influence of exposure to xylenes at 600 ppm for 4 weeks on cytochrome P-450-mediated metabolism of biphenyl and benzo(a)pyrene in male Sprague-Dawley rats. They concluded that xylenes is a phenobarbital-like inducer of rat liver microsomal cytochrome P-450. However, xylenes given subcutaneously to rabbits at 330 or 700 mg/kg per day did not affect DNA synthesis in bone marrow cells or leukocyte, thrombocyte, reticulocyte, or erythrocyte levels in peripheral blood (Speck and Moeschlin, 1968).

Carcinogenicity Studies

Maltoni et al. (1985) administered 500 mg/kg xylenes in olive oil by gavage to 40 male and 40 female 7-week-old Sprague-Dawley rats (4-5 days per week for 104 weeks) and then observed the rats until the animals died. After 141 weeks on test (the end of the study), 1/34 males and 0/36 females had lymphocytic thymomas compared with none in controls; 3/34 males and 3/36 females had hemolymphoreticular neoplasias compared with 3/45 and 1/49 in the controls. At the end of the study, 14/40 dosed males and 22/40 dosed females had malignant (unspecified) lesions compared with 11/50 control males and 10/50 control females. The emphasis of the Maltoni et al. (1985) report is on benzene, and data relative to xylenes exposure are less complete. The report of an increase in the number of total malignant tumors without information on survival and specific tumor type makes evaluation of the results difficult. Also, evaluating carcinogenesis studies by combining tumors of various histogenic origins is not considered to be the best approach (Haseman et al., 1986; McConnell et al., 1986). As in human epidemiology studies, comparison of site-specific neoplasia is the most valid method for evaluating carcinogenic responses in experimental investigations.

In humans, the odor threshold was estimated to be about 1 ppm, but the only sign of discomfort after a 15-minute inhalation period at 460 ppm was eye irritation in four of six subjects (Carpenter et al., 1975). Hipolito (1980) described effects of solvent poisoning for cytotechnicians exposed to xylenes for 1.5-18 years; symptoms and signs included chronic headache, chest pain, electrocardiographic abnormalities, dyspnea, cyanosis of the hands, fever, leukopenia, malaise, impaired lung function, inability to work, and confusion. Dossing et al. (1981) reviewed hospital records of patients referred for suspected solvent poisoning. Liver damage attributed to occupational exposure to organic solvents (including xylenes) was found in 13 patients, but focal necrosis was found only in persons exposed within the previous 6 months. No reduction in the glomerular filtration rate of ^{51}Cr-EDTA was observed in kidney function studies of humans exposed to organic solvents, including xylenes (Askergren et al., 1981a,b,c). However, urinary excretion of red and white blood cells was found to be significantly greater in 101 men occupationally exposed to xylenes and toluene than in controls (Askergren, 1981). Chemical workers occupationally exposed to

xylenes had a significant increase of urinary glucaric acid, which was related to hippuric acid excretion (Dolara et al., 1982).

The toxic effects of xylenes can be summarized as follows (Mackison et al., 1981; Sittig, 1985): Xylenes vapor irritates the eyes, nose, throat, mucous membranes, and skin; at high concentrations, it causes narcosis. Repeated or prolonged dermal contact with xylenes may cause drying and defatting of the skin which, in turn, may lead to dermatitis. Liquid xylenes is also irritating to the eyes and mucous membranes, and aspiration of a few milliliters may cause chemical pneumonitis, pulmonary edema, and hemorrhage. Repeated exposure of the eyes to xylenes at high concentrations may cause irreversible damage. Short-term exposure to xylenes vapor may cause central nervous system depression and minor reversible effects on the liver and kidneys. Inhalation of xylenes at high concentrations may cause dizziness, staggering, drowsiness, and unconsciousness; and inhalation at very high concentrations may cause pulmonary edema, anorexia, nausea, vomiting, and abdominal pain.

Teratogenic and Reproductive Effects

Exposure of pregnant CD rats to air containing 100 or 400 ppm xylenes for 6 hours per day on days 6-15 of gestation resulted in no adverse effects on the mothers and no evidence of fetal sex ratio variation, embryotoxicity, inhibition of fetal growth, or teratogenic potential (API, 1978). Hudak and Ungvary (1978) exposed CFY rats to xylenes at 230 ppm 24 hours per day on days 9-14 of gestation and concluded that xylenes was not teratogenic; however, extra ribs and fused sternebrae were observed.

Ungvary et al. (1980) exposed CFY rats to *o*-, *m*-, or *p*-xylene at 35, 346, or 690 ppm for 24 hours per day during days 7-14 of pregnancy and reported that the solvent crossed the placenta and was found in fetal blood and amniotic fluid. Toxic effects were seen in mothers at the highest concentration, and a dose-dependent retardation of fetal development was observed but not considered a teratogenic effect. In later studies, CFY rats exposed by inhalation to *p*-xylene at 700 ppm on days 10 or 9 and 10 of gestation produced fetuses with lowered body weights and decreased levels of progesterone and 17β-estradiol in peripheral blood. It was concluded that *p*-xylene induced the hepatic monooxygenase system, thus facilitating the metabolism of these two hormones and producing the decrease in peripheral hormone levels (Ungvary et al., 1981).

Pregnant CD-1 mice were gavaged three times per day with xylenes in cottonseed oil at concentrations (v/v) of 0%, 2%, 4%, 8%, 10%, 12%, or 16% (10 ml/kg body weight) on days 6-15 of gestation (Marks et al., 1982). The fetuses from dams exposed at 8% or higher had body weights that were lower than those of the controls, and exposure at these concentrations produced a significantly increased incidence of malformed fetuses, toxic effects (i.e., maternal liver enlargement), and maternal mortality (at 12% and 16%). A study of reproductive effects was conducted in which 90 male and 180 female rats were exposed to xylenes (mixed) by inhalation at 0, 60, 250, or 500 ppm (6 hours per day for 131 premating days, 20 mating days, and most of gestation and lactation for females) (API, 1983). No deaths and no effect on the body weights of premating or maternal rats were observed. However, mid dose males and females and high dose females had significantly lower mating indexes as compared with untreated controls. Pregnancy/fertility indexes between dosed and control animals were comparable, and no adverse dose-related effects were observed on the testes of parents or tissues from high dose pups. A significant increase in mean kidney weight in high dose F_0 parents and a lower mean number of fetuses per litter with malformations were observed in the high-exposure group.

The effects of xylenes exposure on development was recently reviewed by Hood and Ottley (1985). Fetotoxic effects following inhalation exposures to xylenes (mixed) included altered enzyme activities in rat pups. Dermal applications resulted in apparent changes in fetal enzyme activities; oral or inhalation exposure of pregnant rats was followed by mortality, growth inhibition, and malformations. Malformations occurred primarily at concentrations toxic to the mother, and the reviewers concluded that there was no clear evidence for a teratogenic effect from xylenes exposure.

Genetic Toxicology

Xylenes, as well as the individual isomers present in the solvent (*m*-, *o*-, and *p*-xylene) and ethylbenzene, has been tested for mutagenicity in a variety of in vivo and in vitro assays. In general, xylenes is considered to be nonmutagenic.

Salmonella/microsome assays on xylenes, the individual isomers, and ethylbenzene demonstrated no mutagenic activity of the compounds with or without exogenous metabolic activation (Connor et al., 1985; Bos et al., 1981; Florin et al., 1980; Lebowitz et al., 1979). These results were confirmed by NTP studies of xylenes, the individual isomers, and ethylbenzene using the preincubation protocol in *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA97, and TA98 in the presence and absence of S9 from the liver of Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamsters (Haworth et al., 1983; Appendix E).

Xylenes was nongenotoxic in a microsuspension assay developed by McCarroll et al. (1981a) to measure chemically induced growth inhibition resulting from DNA damage to seven repair-deficient strains of *Escherichia coli*. Xylenes was further tested in a microsuspension adaptation to the *Bacillus subtilis rec* assay with strains H17 and M45, designed to detect chemicals that cannot pass unaltered through the cell wall of *E. coli* (McCarroll et al., 1981b). Again, xylenes gave no indication of mutagenic potential.

Analysis in bacterial test systems of xylenes metabolites, specifically the *m*-, *o*-, and *p*-xylenols (dimethylphenols) and the methylbenzyl alcohols also demonstrated no mutagenic activity for these compounds. Various combinations of *S. typhimurium* strains TA100, TA1535, TA1537, TA1538, and TA98, with and without metabolic activation from S9, have been used to test for mutagenic activity of *p*-xylenol (Pool and Lin, 1982; Florin et al., 1980; Epler et al.,1979; Hejtmankova et al., 1979), *m*-xylenols (Florin et al., 1980; Epler et al., 1979), and *o*-methylbenzyl alcohol (Bos et al., 1981). 2,4-Dimethylphenol was ineffective in causing gene reversion in *E. coli* strain Sd-4-73 (Szybalski, 1958).

Donner et al. (1980) tested xylenes, ethylbenzene, *m*-xylene, and *o*-xylene in the Drosophila sex-linked recessive lethal test and found no increase above the spontaneous recessive lethal frequency following exposure to the individual isomers. However, the commercial xylenes mixture did have a weak mutagenic response in this system.

Xylenes was not mutagenic when tested in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay by Lebowitz et al. (1979). Xylenes (mixed) also did not increase the frequency of sister-chromatid exchanges (SCEs) or chromosomal aberrations in cultured human lymphocytes (Gerner-Smidt and Friedrich, 1978). The results from the chromosomal aberration study must be qualified, however, because the authors scored only 60 metaphases instead of the 100 metaphases usually analyzed in this test.

In vivo mutagenicity testing of xylenes consists of rat bone marrow chromosomal aberration studies. Donner et al. (1980) exposed rats by inhalation to xylenes at 300 ppm 6 hours per day, 5 days per week, for 9-18 weeks and found no increase in the frequency of chromosomal aberrations. Lebowitz et al. (1979) found no evidence of clastogenic activity in the bone marrow of rats following intraperitoneal administration of commercial xylenes.

The presence of a large amount (17%) of ethylbenzene in xylenes somewhat complicates the investigation of the mutagenic potential of xylenes. Ethylbenzene is nonmutagenic when tested in a gene reversion assay using *Saccharomyces cerevisiae* strains D7 and XV185-14C without S9 (Nestmann and Lee, 1983). In the Salmonella/microsome assay with strains TA100, TA1535, TA1537, TA1538, and TA98, ethylbenzene did not increase the number of histidine-revertant colonies either in the presence or absence of exogenous metabolic activation by S9 (Nestmann et al., 1980; Florin et al., 1980). As previously noted, NTP studies confirm these results in Salmonella. Also previously noted, ethylbenzene was nonmutagenic when tested in the Drosophila recessive lethal test by Donner et al. (1980). Norppa and Vainio (1983) tested the ability of ethylbenzene to induce SCEs in cultured human lymphocytes. At the highest dose tested (10 mM), which was toxic, ethylbenzene

induced a slight but statistically significant ($P<0.01$) increase in the number of SCEs. The overall response curve demonstrated a dose-dependent relationship. The authors concluded that ethylbenzene is a "weak, ineffective mutagen." In vitro cytogenetic tests conducted by the NTP demonstrated no mutagenic activity for ethylbenzene in cultured Chinese hamster ovary (CHO) cells with or without metabolic activation from Aroclor 1254-induced male Sprague-Dawley rat liver S9; neither the frequency of sister-chromatid exchanges nor of chromosomal aberrations was affected (Appendix E, Tables E6 and E7). Although the highest dose used in the NTP studies was approximately tenfold lower than that used by Norppa and Vainio (1983), this concentration also approached toxic levels for CHO cells.

Study Rationale

Xylenes (mixed) was nominated for toxicology and carcinogenesis studies by the Consumer Products Safety Commission, U.S. Environmental Protection Agency, National Cancer Institute, and the National Institute for Occupational Safety and Health. Xylenes was selected because of its large annual production, significant worker exposure, potential consumer exposure, and a lack of adequate long-term carcinogenicity studies in animals or epidemiologic studies in humans. Humans can be exposed to xylenes by inhalation, by dermal contact, and increasingly by ingestion because of ground water contamination. To obtain a precise measure of dose, the gavage route of exposure was selected for the present NTP studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF XYLENES (MIXED)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF XYLENES (MIXED)

Xylenes (mixed) was obtained from the Shell Oil Company (Houston, Texas) in a single lot (lot no. F-309), which was used for all studies. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (MRI, 1979, 1980).

This lot was obtained as a clear, colorless liquid with a boiling point of 137° C. The identity of xylenes (mixed) was confirmed by elemental analysis and infrared (Figure 2), ultraviolet/visible, and nuclear magnetic resonance (Figure 3) analyses. All data were consistent with the composition of mixed xylene isomers and ethylbenzene.

Analysis indicated that lot no. F-309 contained 17.0% ethylbenzene, 13.6% *p*-xylene, and 60.2% *m*-xylene and 9.1% *o*-xylene. This composition of xylene isomers and ethylbenzene was confirmed by analysis conducted by the manufacturer. Less than 0.3% of other volatile impurities was present. The following purity assessment data was generated for lot no. F-309. The elemental analysis for carbon was slightly high, whereas that for hydrogen agreed with the theoretical value. Water content was 0.10% by Karl Fischer titration. Gas chromatography gave four major peaks and five impurity peaks (0.26%) on one gas chromatographic system and three major peaks and three impurity peaks (0.12%) on a second system. The major peaks were identified by spiking with ethylbenzene, *p*-xylene, *m*-xylene, and *o*-xylene standards. (*p*-Xylene and *m*-xylene were unresolved by the second system.) Quantitation of benzene in lot no. F-309 was also determined by gas chromatography to be less than 5.0 ppm. The manufacturer reported this lot of xylenes contained 2.8 ppm benzene.

The study material was determined to be stable when stored for 2 weeks at 60° C. Therefore, the study material was stored at ambient temperatures for the duration of the toxicity studies. Periodic characterization of the xylenes study material and a reference standard stored at −20° C by infrared spectroscopy and gas chromatography indicated no degradation over the course of the toxicity studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Accurately weighed amounts of xylenes and corn oil were mixed to give the desired concentrations (Table 1). The stability of xylenes in corn oil was analyzed by gas chromatography with flame

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF XYLENES (MIXED)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation Weighed portions of xylenes (mixed) were placed in a graduated cylinder and mixed with corn oil to achieve the proper volume. The mixtures were shaken vigorously for 10 seconds.	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Maximum Storage Time 2 wk	2 wk	2 wk	2 wk
Storage Conditions 23° C	23° C	23° C	Approximately 24° C, 45% humidity under fluorescent light

Instrument: Beckman IR-12
Cell: Neat liquid between silver chloride plates

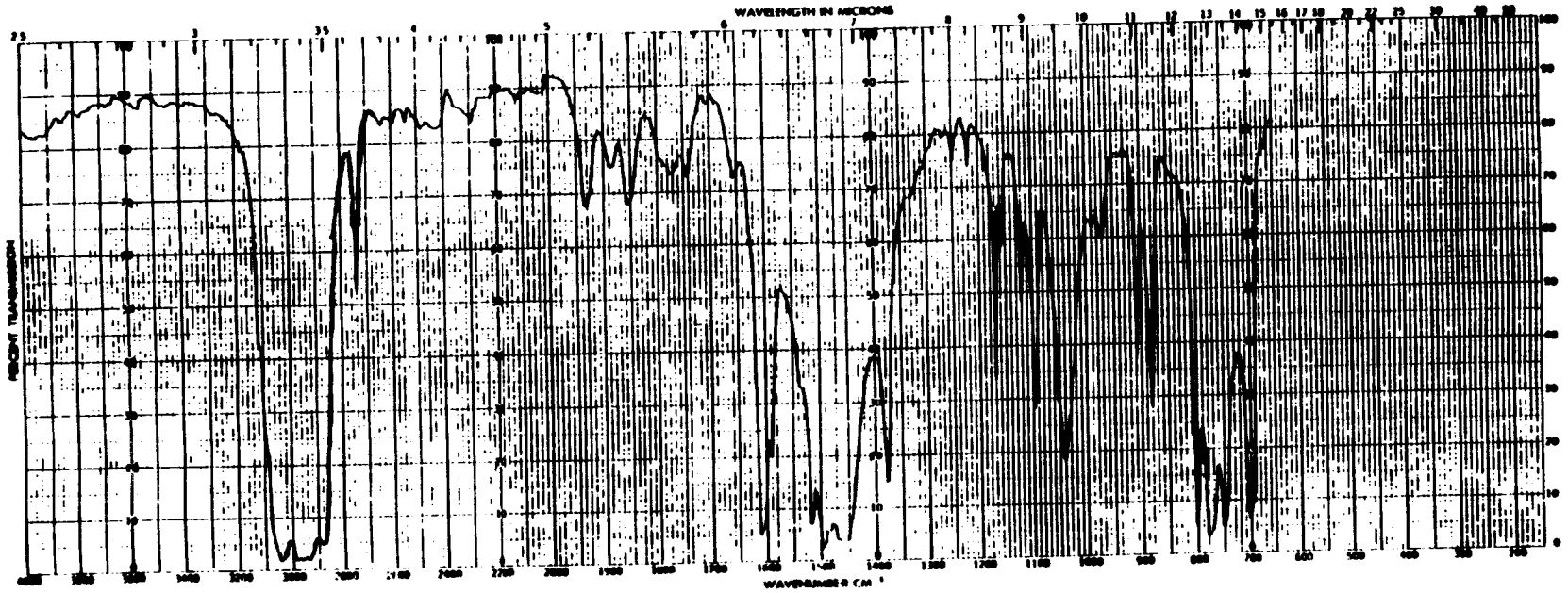


FIGURE 2. INFRARED ABSORPTION SPECTRUM OF XYLENES (MIXED) (LOT NO. F-309)

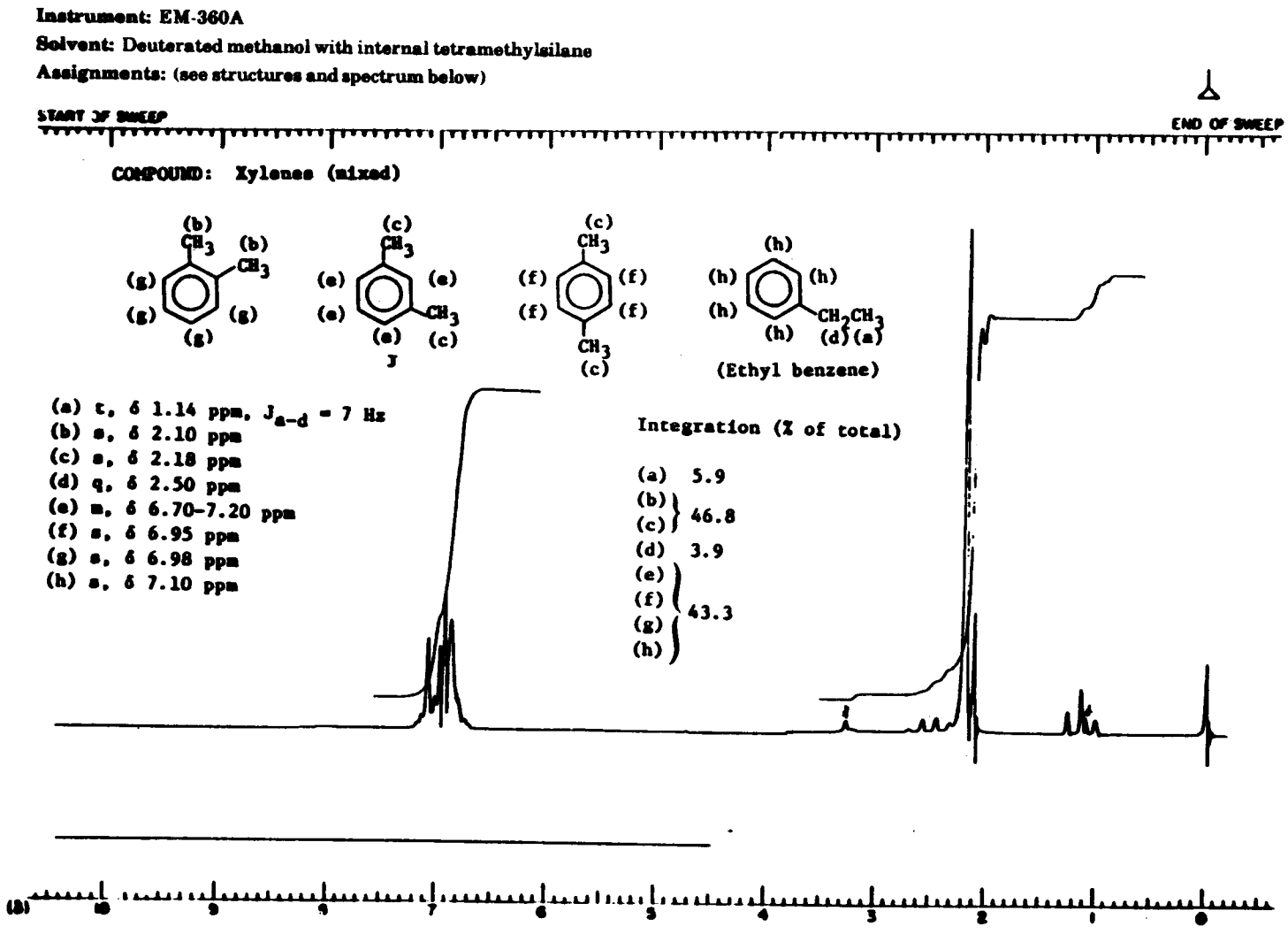


FIGURE 3. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF XYLENES (MIXED) (LOT NO. F-309)

ionization detection following extraction with methanol. All four major components of xylenes were found to be stable in corn oil for at least 7 days at room temperature. Formulated xylenes/corn oil mixtures were stored at 24° C for no longer than 2 weeks.

Periodic analyses of formulated xylenes/corn oil dose mixtures by methanolic extraction and gas chromatography were performed at the study and analytical chemistry laboratories to determine if the dose mixtures contained the correct concentrations of xylenes. Dose mixtures were analyzed once during the 13-week studies. The results ranged from 84.8% to 107.5% of the target concentrations (Table 2). During the 2-year studies, the dose preparations were analyzed once every 2 months, with concentrations varying from 94.6% to 106.9% (Table 3). Because all dose mixtures analyzed for the 2-year studies were within 10% of the target concentrations, the other dose mixtures were estimated to have been within specifications throughout the studies. Referee analyses were periodically performed by an independent laboratory. Good agreement was generally found between laboratories (Table 4).

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 18 days before the studies began. Groups of five rats and five mice of each sex were administered a single dose of 500, 1,000, 2,000, 4,000, or 6,000 mg/kg xylenes in corn oil by gavage. No controls were used.

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF XYLENES (MIXED)

Target Concentration (a) (mg/ml)	Determined Concentration (b) (mg/ml)	Percent of Target
(c) 250 R	243.70	97.5
(c) 250 M	244.48	97.8
125 R	129.40	103.5
125 M	134.33	107.5
62.5 R	64.67	103.5
62.5 M	62.13	99.4
31.25 R	30.36	97.2
31.25 M	26.49	84.8
15.63 R	16.57	106.0
15.63 M	15.71	100.5

(a) Date mixed: 09/27/79
(b) Results of duplicate analysis
(c) R and M specify rat and mouse formulations.

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

Date Mixed	Concentration (a) of Xylenes (Mixed) in Corn Oil for Target Concentration (mg/ml)	
	62.5	125
07/14/80	64.4	132.2
09/05/80	65.6	131.0
10/30/80	59.1	119.6
12/18/80	61.9	129.7
02/20/81	62.4	123.4
04/16/81	62.1	122.2
06/12/81	66.7	123.1
08/21/81	63.0	128.9
10/22/81	66.8	127.7
12/17/81	66.3	127.0
02/04/82	64.2	125.0
04/01/82	61.7	122.1
06/04/82	60.0	128.4
Mean (mg/ml)	63.4	126.2
Standard deviation	2.51	3.89
Coefficient of variation (percent)	3.96	3.08
Range (mg/ml)	59.1-66.8	119.6-132.2
Number of samples	13	13

(a) Results of duplicate analysis

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
09/05/80	125	131.0	127.6
02/20/81	125	123.4	126.8
08/21/81	62.5	63.0	62.9
02/04/82	125	125.0	121.9

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

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 5. The animals were observed twice daily for 14 days and were killed on day 16. Final mean body weights were not recorded. A necropsy was not performed.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 13 days before the studies began. Groups of five rats of each sex were administered 125, 250, 500, 1,000, or 2,000 mg/kg xylenes in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex received 250, 500, 1,000, 2,000, or 4,000 mg/kg on the same schedule. Controls were untreated.

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 5. The animals were observed twice daily and were weighed on days 0 and 14. A necropsy was performed on all animals.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF XYLENES (MIXED)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
500, 1,000, 2,000, 4,000, or 6,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--8 ml/kg	Rats--125, 250, 500, 1,000, or 2,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--4 ml/kg; mice--250, 500, 1,000, 2,000, or 4,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--8 ml/kg; controls were untreated.	Rats--0, 62.5, 125, 250, 500, or 1,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--4 ml/kg; mice--0, 125, 250, 500, 1,000, or 2,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--8 ml/kg	Rats--0, 250, or 500 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--4 ml/kg; mice--0, 500, or 1,000 mg/kg xylenes (mixed) in corn oil by gavage; dose vol--8 ml/kg
Date of First Dose			
3/5/79	5/17/79	8/6/79	Rats--6/30/80; mice--7/21/80
Date of Last Dose			
N/A	5/30/79	11/2/79	Rats--6/18/82; mice--7/9/82
Duration of Dosing			
One time only	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d	Observed 2 × d; clinical signs recorded 2 × d	Observed 2 × d; body weight recorded 1 × wk	Observed 2 × d; clinical signs recorded 1 × d for 16 mo, then 1 × mo; weighed 1 × wk for 12 wk, then 1 × 4 wk
Necropsy and Histologic Examination			
No necropsy or histologic exams performed	Necropsy performed on all animals; histologic exams not performed	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: gross lesions and tissue masses, mandibular lymph node, salivary gland, sternebrae, femur, or vertebrae including marrow, thyroid gland, parathyroids, small intestine, colon, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, liver, gallbladder (mice), prostate/testis or ovaries/uterus, lungs and mainstem bronchi, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs present), eyes (if grossly abnormal), and mammary gland	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, mandibular lymph nodes, salivary gland, femur, including marrow, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testis or ovaries/uterus, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, skin, lungs and mainstem bronchi, kidneys, adrenal glands, urinary bladder, pituitary gland, eyes (if grossly abnormal), and mammary gland

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF XYLENES (MIXED) (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Same as single-administration studies	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification			
Toe clip	Toe clip	Toe clip	Toe clip
Time Held Before Study			
18 d	13 d	15 d	19 d
Age When Placed on Study			
7 wk	Rats--6 wk; mice--7 wk	Rats--6 wk; mice--7 wk	Rats--7 wk; mice--8 wk
Age When Killed			
9 wk	Rats--8 wk; mice--9 wk	19 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy Dates			
N/A	Rats--5/31/79; mice--6/1/79	Rats--11/5/79-11/6/79; mice--11/6/79-11/7/79	Rats--6/28/82-7/2/82; mice--7/19/82-7/23/82
Method of Animal Distribution			
Randomized to cages by one random numbers table, then to groups by another table	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed			
Purina Lab Chow® (Ralston Purina Co., St. Louis, MO)	Same as single-administration studies	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum, except 7/2/81-7/9/81: Purina Lab Chow®
Bedding			
Absorb-Dri® (Lab Products, Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration	Same as single-administration studies
Cage Filters			
Reemay® spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF XYLENES (MIXED) (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--22° ± 1°C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Same as single-administration studies	Temp--23° ± 1°C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of xylenes and to determine the doses to be used in the 2-year studies. Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 2 weeks, and then assigned to study groups according to a table of random numbers.

Groups of 10 rats of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg xylenes (mixed) in corn oil, 5 days per week, for 13 weeks. Groups of 10 mice of each sex were administered 0, 125, 250, 1,000, or 2,000 mg/kg on the same schedule.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5. Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 250, or 500 mg/kg xylenes in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 500, or 1,000 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 5 weeks of age and mice at 6 weeks. The animals were quarantined at the study laboratory for 19 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 8 weeks. The health of the animals was monitored during the

course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but the results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. At the end of the quarantine period, animals were individually weighed to determine the weight range for each sex. Animals were distributed by sex from weight classes to cage groups of five animals each, and 10 cages were then assigned to the dosed and vehicle control groups and three cages to the sentinel group according to tables of random numbers. Animals were then weighed and numbered by toe clip to identify individuals and their study group. Cages and racks were not rotated during this study. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per day for 16 months and then once per month. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed, cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment laboratory. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those for which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the

laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless lesions in question are subtle or unless there is inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

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

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to

obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the studies were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

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III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

All the rats that received 6,000 mg/kg and 3/5 males that received 4,000 mg/kg died within 48 hours of dosing (Table 6). Lack of coordination, prostration, loss of hindleg movement, and hunched posture were detected within 24 hours of dosing in male and female rats that received 4,000 or 6,000 mg/kg. Male and female rats that received 2,000 mg/kg had rough coats. No clinical signs of toxicity were noted in the surviving animals at the end of week 1. Body weight gain was decreased in the higher dose groups.

FOURTEEN-DAY STUDIES

Three of five male and five of five female rats that received 2,000 mg/kg died before the end of the studies (Table 7). Two other deaths were considered to be due to gavage trauma. The change in mean body weight relative to that of controls was 23%-29% lower for males that received 250, 500, and 1,000 mg/kg and 17% and 26% lower for females that received 125 and 1,000 mg/kg after 14 days. Shallow, labored breathing and prostration were observed immediately after dosing for male and female rats that received 2,000 mg/kg. No compound-related effects were observed at necropsy.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)		
		Initial	Final	Change
MALE (b)				
500	5/5	189	244	+ 55
1,000	5/5	185	232	+ 47
2,000	5/5	183	234	+ 51
4,000	2/5	178	213	+ 35
6,000	0/5	181	(c)	(c)
FEMALE				
500	5/5	131	154	+ 23
1,000	5/5	136	157	+ 21
2,000	5/5	127	146	+ 19
4,000	5/5	130	147	+ 17
6,000	0/5	137	(c)	(c)

(a) Number surviving/number initially in the group; all deaths occurred within 48 hours of dosing.
(b) LD_{50} by Spearman-Karber procedure, 3,523 mg/kg with 95% confidence interval of 2,707-4,587 mg/kg
(c) No data are reported due to the 100% mortality in this group.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	190	242	+52	--
125	(d) 4/5	186	235	+49	97.1
250	5/5	184	222	+38	91.7
500	5/5	180	220	+40	90.9
1,000	5/5	195	232	+37	95.9
2,000	(e) 2/5	192	198	+6	81.8
FEMALE					
0	5/5	132	155	+23	--
125	5/5	133	152	+19	98.1
250	(f) 4/5	139	163	+24	105.2
500	5/5	140	162	+22	104.5
1,000	5/5	132	149	+17	96.1
2,000	(g) 0/5	130	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial mean group body weight
(c) Mean body weight change of the group
(d) Day of death: 1 (gavage related)
(e) Day of death: 2, 2, 4
(f) Day of death: 6 (gavage related)
(g) Day of death: 2, 2, 2, 2, 3
(h) No data are reported due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

All the rats survived to the end of the studies (Table 8). The change in mean body weight of male and female rats that received 1,000 mg/kg was 15% and 8% lower than that of the vehicle controls after 13 weeks of exposure. No signs of toxicity were observed, and no compound-related gross or microscopic pathologic lesions were observed.

Dose Selection Rationale: Based on weight gain depression at 1,000 mg/kg in both sexes in the 14-day studies and in males in the 13-week studies and on the clinical signs in the 14-day studies, doses selected for rats for the 2-year studies were 0, 250, and 500 mg/kg xylenes (mixed) in corn oil by gavage, administered 5 days per week.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	89 ± 2	328 ± 5	+ 239 ± 4	--
62.5	10/10	87 ± 2	323 ± 4	+ 236 ± 4	98
125	10/10	85 ± 1	327 ± 8	+ 242 ± 9	100
250	10/10	86 ± 2	315 ± 9	+ 229 ± 9	96
500	10/10	89 ± 2	330 ± 9	+ 241 ±10	101
1,000	10/10	87 ± 2	291 ± 7	+ 204 ± 7	89
FEMALE					
0	10/10	83 ± 3	190 ± 3	+ 107 ± 3	--
62.5	10/10	86 ± 3	201 ± 2	+ 115 ± 2	106
125	10/10	90 ± 2	208 ± 2	+ 118 ± 3	109
250	10/10	85 ± 2	193 ± 3	+ 108 ± 2	102
500	10/10	86 ± 2	198 ± 4	+ 112 ± 3	104
1,000	10/10	86 ± 2	184 ± 4	+ 98 ± 4	97

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-8% lower than those of the vehicle controls after week 59 (Table 9 and Figure 4). Mean body weights of low dose and vehicle control male rats and dosed and vehicle control female rats were comparable throughout most of the studies.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	250 mg/kg Av. Wt. (grams)	250 mg/kg Wt. (percent of veh. controls)	250 mg/kg No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors
MALE								
0	143	50	145	101	50	143	100	50
2	193	50	196	102	50	197	102	50
3	220	50	225	102	50	223	101	50
4	241	50	244	101	50	243	101	50
5	257	50	260	101	50	258	100	50
6	281	50	284	101	50	279	99	50
7	297	50	300	101	50	297	100	50
8	306	50	308	101	50	307	100	50
9	315	50	316	100	50	318	101	50
10	326	50	324	99	50	325	100	50
11	334	50	334	100	50	335	100	50
12	343	50	342	100	50	341	99	50
16	370	50	368	99	50	363	98	50
20	395	50	394	100	50	389	98	50
24	413	50	410	99	50	411	100	50
29	424	50	420	99	49	416	98	49
34	438	50	428	98	49	429	98	49
38	452	50	446	99	49	440	97	49
42	466	50	458	98	49	449	96	48
46	475	50	466	98	48	455	96	44
50	477	50	467	98	48	456	96	43
54	482	50	472	98	47	459	95	43
59	479	50	472	99	46	464	97	42
64	482	48	473	98	46	459	95	41
68	484	48	476	98	44	459	95	41
73	482	48	486	101	41	456	95	41
77	493	45	485	98	40	461	94	39
80	493	45	486	99	40	466	95	37
84	487	42	477	98	37	457	94	33
88	494	41	484	98	33	469	95	30
93	479	41	464	97	32	455	95	29
97	473	38	453	96	29	437	92	27
103	452	36	428	95	26	434	96	20
FEMALE								
0	114	50	116	102	50	115	101	50
2	141	50	141	100	50	142	101	50
3	151	50	153	101	49	153	101	50
4	159	50	160	101	49	160	101	50
5	167	50	167	100	49	168	101	50
6	176	50	177	101	49	175	99	50
7	181	50	182	101	49	180	99	50
8	183	50	185	101	49	182	99	50
9	187	50	191	102	49	187	100	50
10	189	50	193	102	49	191	101	50
11	191	50	193	101	49	193	101	50
12	194	50	198	102	49	193	99	50
16	204	50	206	101	49	204	100	50
20	211	50	212	100	49	211	100	50
24	216	50	219	101	49	218	101	50
29	219	50	222	101	49	220	100	50
34	228	50	229	100	49	227	100	50
38	237	50	240	101	49	235	99	50
42	244	50	245	100	49	243	100	49
46	250	50	251	100	49	249	100	49
50	255	50	255	100	49	253	99	49
54	263	50	262	100	49	261	99	49
59	269	50	265	99	49	268	100	49
64	278	50	274	99	49	272	98	49
68	287	50	284	99	48	279	97	49
73	295	50	292	99	47	290	98	48
77	300	50	301	100	47	297	99	48
80	307	47	308	100	46	306	100	47
84	298	47	304	102	44	302	101	47
88	307	44	314	102	43	312	102	45
93	316	42	314	99	42	312	99	44
97	316	41	311	98	41	311	98	40
103	315	39	317	101	33	308	98	36

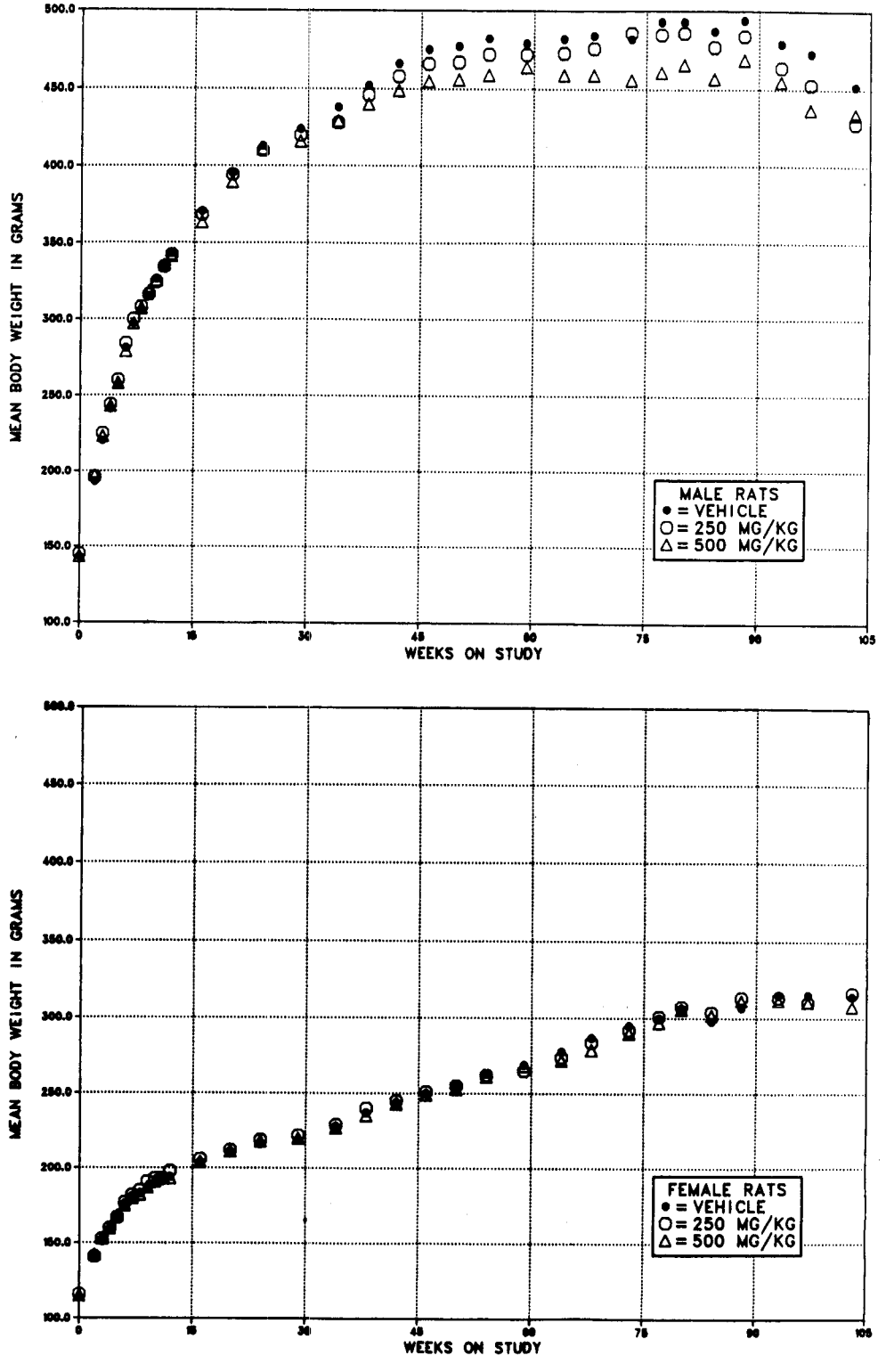

FIGURE 4. GROWTH CURVES FOR RATS ADMINISTERED XYLENES (MIXED) IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered xylenes (mixed) at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 5. The survival of the high dose group of male rats was significantly lower than that of the vehicle controls after week 103 (Table 10). No other differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the testis, hematopoietic system, and pituitary gland.

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

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

TABLE 10. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

	Vehicle Control	250 mg/kg	500 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	16	19
Accidentally killed	3	8	11
Killed at termination	36	25	20
Died during termination period	0	1	0
Survival P values (c)	0.033	0.204	0.040
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	15	13
Accidentally killed	0	2	1
Killed at termination	38	33	35
Died during termination period	1	0	1
Survival P values (c)	0.744	0.478	0.822

(a) Terminal-kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

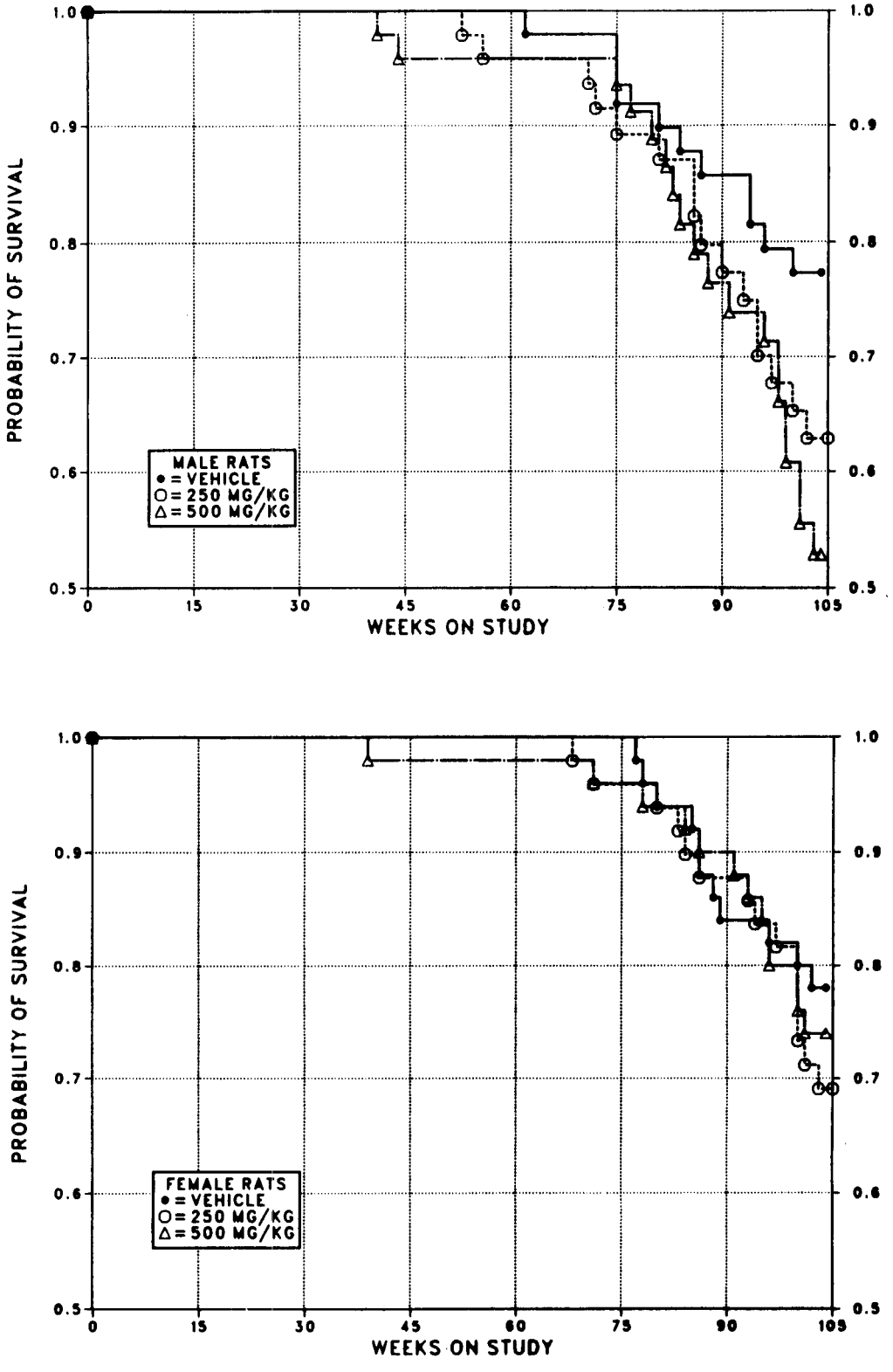

FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED XYLENES (MIXED) IN CORN OIL BY GAVAGE FOR TWO YEARS

Testis: Although the overall incidences of interstitial cell tumors were comparable in male rat groups (vehicle control, 43/50; low dose, 38/50; high dose, 41/49), survival-adjusted analyses indicated an increased incidence in the high dose group relative to vehicle controls (Appendix A, Table A3). This apparent effect was due primarily to animals dying between weeks 62 and 92, for which the incidence of interstitial cell tumors was 13/13 for the high dose group compared with 4/9 for vehicle controls. Tumor incidences were comparable during the other time intervals. It is doubtful that this marginal effect is compound related.

Hematopoietic System and Pituitary Gland: Dose-related decreases in the incidences of mononuclear cell leukemia (vehicle control, 22/50; low dose, 18/50; high dose, 11/50) and pituitary gland adenoma or carcinoma (combined) (vehicle control, 24/49; low dose, 22/50; high dose, 12/45) were observed in male rats. However, these differences were due primarily to decreased survival of the high dose group relative to that of the vehicle controls (Appendix A, Table A3).

SINGLE-ADMINISTRATION STUDIES

Three of five males and four of five females that received 6,000 mg/kg died before the end of the studies (Table 11). Tremors, prostration, and/or slowed breathing were observed within 48 hours of dosing with 4,000 or 6,000 mg/kg. Final body weights were not dose related.

FOURTEEN-DAY STUDIES

All male and female mice that received 4,000 mg/kg died on the second day of dosing (Table 12). All other animals survived to the end of the studies. Male mice that received 2,000 mg/kg gained notably less weight than did the controls. Female mice that received 2,000 mg/kg gained more weight than did the controls. During week 1, prostration and shallow breathing were observed after dosing in mice that received 2,000 mg/kg.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)		
		Initial	Final	Change
MALE				
500	5/5	25.4	26.8	+ 1.4
1,000	5/5	25.8	27.8	+ 2.0
2,000	5/5	27.4	30.2	+ 2.8
4,000	5/5	26.6	29.4	+ 2.8
6,000	(b) 2/5	28.4	30.0	+ 1.6
FEMALE				
500	5/5	20.0	21.6	+ 1.6
1,000	5/5	19.6	21.2	+ 1.6
2,000	5/5	19.6	21.0	+ 1.4
4,000	5/5	19.0	21.4	+ 2.4
6,000	(c) 1/5	19.4	21.0	+ 1.6

(a) Number surviving/number in group; estimated LD_{50} value by Spearman-Karber procedure (95% confidence interval): male--5,627 mg/kg (4,765-6,646 mg/kg); female--5,251 mg/kg (4,583-6,014 mg/kg).
(b) Deaths occurred within 24 hours of dosing.
(c) Two deaths occurred within 24 hours of dosing and two within 32 hours of dosing.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	23.0	26.8	+ 3.8	--
250	5/5	22.8	24.0	+ 1.2	89.6
500	5/5	23.6	26.4	+ 2.8	98.5
1,000	5/5	23.0	25.6	+ 2.6	95.5
2,000	5/5	24.6	25.0	+ 0.4	93.3
4,000	(d) 0/5	23.0	(e)	(e)	(e)
FEMALE					
0	5/5	19.8	21.8	+ 2.0	--
250	5/5	18.4	19.6	+ 1.2	89.9
500	5/5	19.2	20.8	+ 1.6	95.4
1,000	5/5	18.2	21.2	+ 3.0	97.2
2,000	5/5	18.8	21.6	+ 2.8	99.1
4,000	(d) 0/5	20.6	(e)	(e)	(e)

(a) Number surviving/number in group
(b) Initial mean body weight of the group
(c) Mean weight change of the group
(d) Day of death: all 2
(e) No data are reported due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

Two female mice that received 2,000 mg/kg died before the end of the studies (Table 13); gavage error could not be discounted. Weakness, lethargy, short and shallow breathing, unsteadiness, tremors, and paresis were observed in the 2,000 mg/kg group 5-10 minutes after dosing and lasted 15-60 minutes. Mean body weight gain of mice that received 2,000 mg/kg was 7% lower than that of the vehicle controls for males and 17% lower for females. No compound-related gross or microscopic pathologic lesions were observed.

Dose Selection Rationale: Based on weight gain depression observed at 2,000 mg/kg in the 14-day study (males) and 13-week study (females) and on clinical signs, doses selected for mice for the 2-year studies were 0, 500, and 1,000 mg/kg xylenes (mixed) in corn oil by gavage administered 5 days per week.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF XYLENES (MIXED)

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.2 ± 0.9	32.3 ± 1.2	+ 7.1 ± 0.5	--
125	10/10	24.9 ± 0.7	32.8 ± 1.2	+ 7.9 ± 0.8	101.5
250	10/10	25.5 ± 0.4	33.8 ± 0.6	+ 8.3 ± 0.7	104.6
500	10/10	24.2 ± 0.6	34.3 ± 1.0	+ 10.1 ± 0.8	106.2
1,000	10/10	24.0 ± 0.6	31.6 ± 1.0	+ 7.6 ± 0.8	97.8
2,000	10/10	24.5 ± 0.7	31.1 ± 0.9	+ 6.6 ± 0.5	93.0
FEMALE					
0	10/10	19.5 ± 0.4	25.3 ± 0.3	+ 5.8 ± 0.3	--
125	10/10	19.8 ± 0.4	26.8 ± 0.6	+ 7.0 ± 0.4	105.9
250	10/10	20.3 ± 0.2	26.7 ± 0.5	+ 6.4 ± 0.3	105.5
500	10/10	19.3 ± 0.4	25.4 ± 0.5	+ 6.1 ± 0.3	100.4
1,000	10/10	20.5 ± 0.5	25.7 ± 0.4	+ 5.2 ± 0.6	101.6
2,000	(d) 8/10	19.7 ± 0.4	24.4 ± 0.6	+ 4.9 ± 0.3	96.4

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 5, 10

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed mice were comparable to those of the vehicle controls throughout most of the studies (Table 14 and Figure 6).

Hyperactivity occurred in all high dose (1,000 mg/kg) mice of each sex 5-30 minutes after dosing and was observed consistently during weeks 4-103 of the studies.

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	24.8	50	25.1	101	50	24.6	99	50
1	26.9	50	26.1	97	50	27.0	100	50
2	27.7	50	27.5	99	50	28.0	101	50
3	28.5	50	28.7	101	50	28.9	101	50
4	29.5	50	29.8	101	50	29.8	101	50
5	30.3	50	29.9	99	50	30.5	101	50
7	31.2	50	31.0	99	50	30.8	99	50
8	31.8	50	31.5	99	50	31.2	98	50
9	32.4	50	32.3	100	50	32.2	99	50
10	32.8	50	33.0	101	50	32.4	99	49
11	32.6	50	33.1	102	50	32.0	98	49
12	31.7	50	31.9	101	50	32.2	102	48
16	34.1	48	34.2	100	50	32.6	96	48
20	34.6	47	33.7	97	49	33.6	97	46
24	35.3	47	36.3	103	48	35.5	101	46
29	36.8	47	37.2	101	48	36.8	100	46
34	38.1	47	38.4	101	48	38.0	100	45
37	39.4	47	40.2	102	48	39.8	101	45
41	39.7	47	40.2	101	48	39.0	98	44
46	40.2	47	42.3	105	48	41.2	102	44
50	42.7	46	42.9	100	48	42.4	99	44
54	43.4	45	44.1	102	48	43.1	99	44
59	41.5	45	44.0	106	48	42.2	102	44
63	41.8	45	43.8	105	48	41.9	100	43
68	41.5	44	43.0	104	48	41.1	99	43
72	42.3	44	43.5	103	48	40.8	96	43
76	42.1	44	43.7	104	48	41.5	99	43
80	41.0	42	42.4	103	46	40.6	99	42
84	40.3	38	42.4	105	42	40.7	101	41
89	39.8	34	42.6	107	42	39.5	99	40
93	41.9	32	43.3	103	41	40.8	97	40
98	39.4	31	41.8	106	38	39.8	101	38
103	37.6	28	41.1	109	35	38.7	103	36
FEMALE								
0	18.8	50	18.8	100	50	19.2	102	50
1	20.6	50	20.8	101	50	21.0	102	50
2	21.8	50	21.6	99	50	21.4	98	50
3	22.5	50	22.2	99	50	21.9	97	50
4	23.3	50	23.1	99	50	23.4	100	50
5	24.4	50	24.2	99	50	23.7	97	50
7	24.3	50	24.3	100	50	24.1	99	50
8	24.7	50	24.4	99	50	24.6	100	50
9	24.9	50	24.9	100	50	25.0	100	50
10	25.1	50	24.6	98	50	24.9	99	50
11	25.3	50	24.9	98	50	24.9	98	50
12	24.7	50	24.4	99	50	25.2	102	50
16	26.6	50	26.1	98	50	26.3	99	50
20	27.3	50	26.6	97	50	27.0	99	50
24	27.8	50	27.4	99	50	28.5	103	50
29	29.3	50	29.1	99	50	29.5	101	50
34	29.7	50	29.4	99	50	28.8	97	50
37	31.0	50	31.2	101	50	30.8	99	50
41	33.0	50	31.8	96	50	31.9	97	50
46	33.7	50	33.6	100	50	33.7	100	50
50	34.4	50	35.0	102	50	34.4	100	50
54	35.3	50	33.2	94	50	33.1	94	50
59	35.1	50	35.0	100	50	34.8	99	50
63	35.9	50	35.0	97	50	35.0	97	50
68	37.1	49	35.7	96	50	35.3	95	48
72	37.9	47	37.6	99	50	35.7	94	47
76	37.0	45	37.5	101	50	35.8	97	47
80	36.3	45	36.6	101	49	35.7	98	45
84	36.2	44	36.1	100	49	35.3	98	43
89	36.9	43	35.3	96	46	35.6	96	41
93	35.2	42	35.5	101	44	35.9	102	40
98	36.4	38	36.1	99	43	35.2	97	34
103	37.1	36	34.3	92	36	35.4	95	31

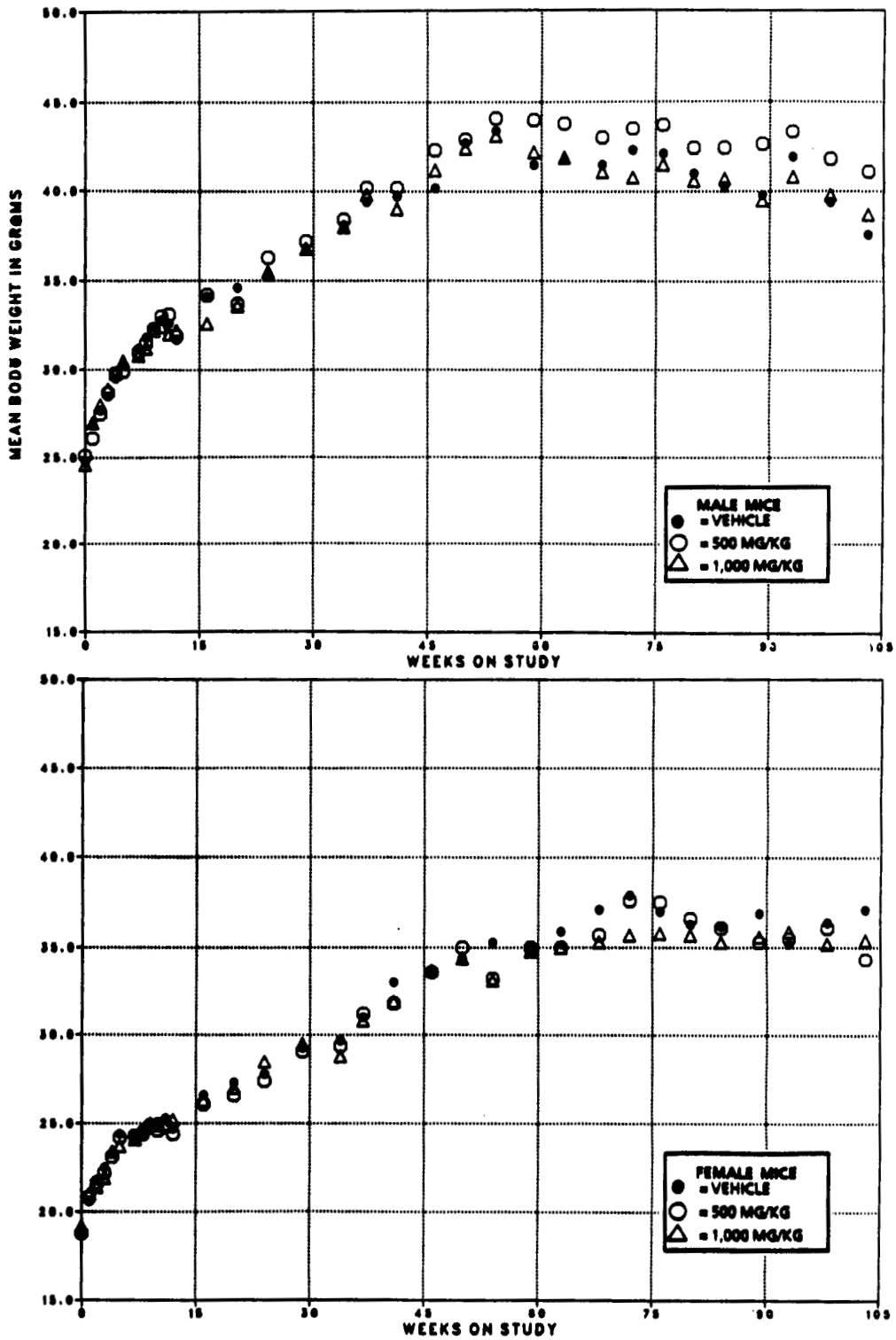

FIGURE 6. GROWTH CURVES FOR MICE ADMINISTERED XYLENES (MIXED) IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered xylenes (mixed) at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 7. No significant differences in survival were observed between any groups of either sex (Table 15).

Pathology and Statistical Analyses of Results

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

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

No significant nonneoplastic or neoplastic effects were observed in male or female mice.

TABLE 15. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED)

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	15	11
Accidentally killed	1	0	3
Animals missing	2	0	0
Killed at termination	27	35	36
Died during termination period	1	0	0
Survival P values (c)	0.106	0.370	0.137
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	14	14	19
Killed at termination	36	35	31
Died during termination period	0	1	0
Survival P values (c)	0.357	0.877	0.443

(a) Terminal-kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

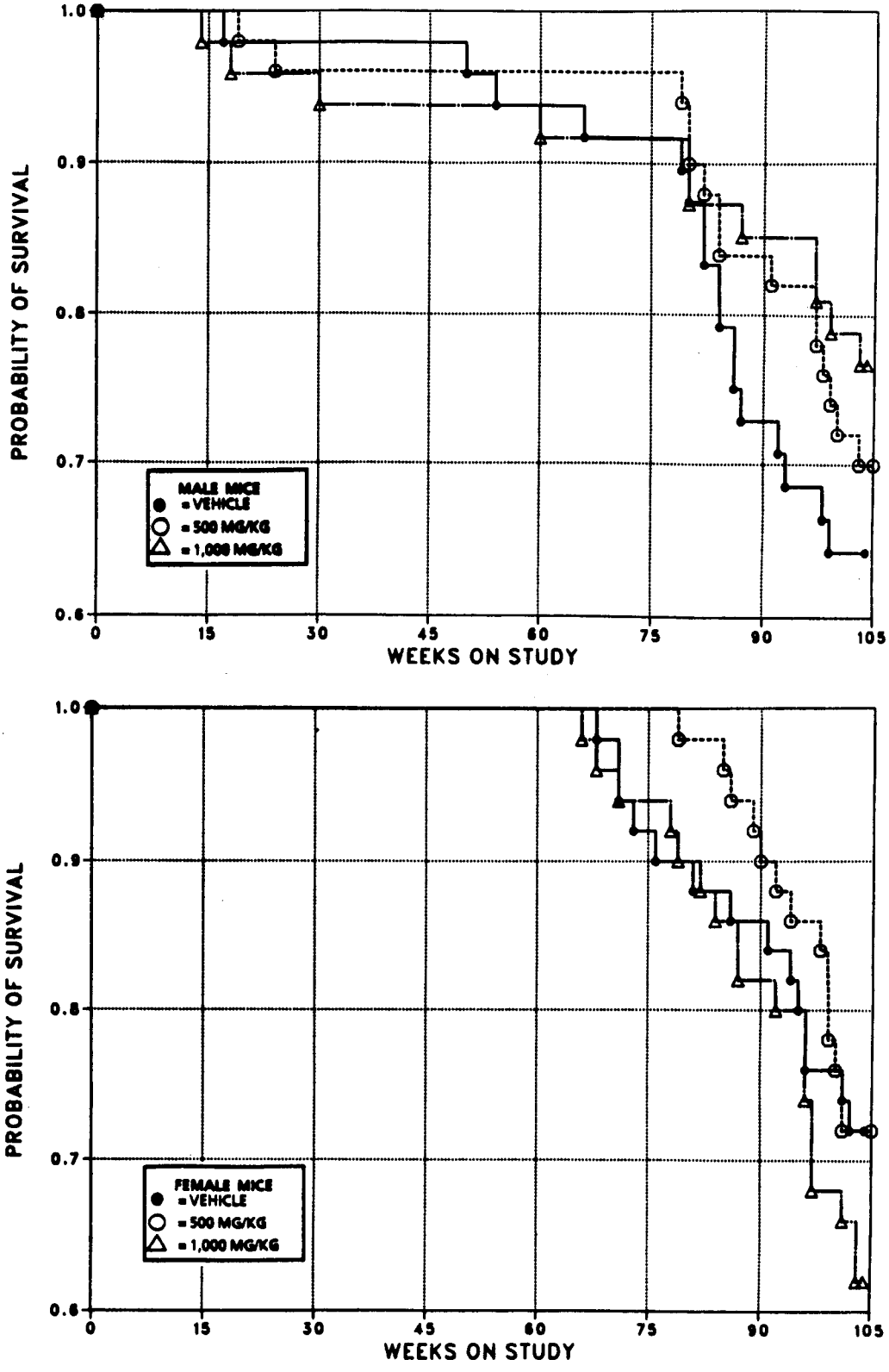

FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED XYLENES (MIXED) IN CORN OIL BY GAVAGE FOR TWO YEARS

IV. DISCUSSION AND CONCLUSIONS

Doses selected for the 2-year studies were based on the results of the short-term studies. Thus, deaths at 4,000 and 6,000 mg/kg for rats and mice of each sex in the single-administration and 14-day studies and at 2,000 mg/kg for male and female rats in the 14-day studies and female mice in the 13-week studies restricted the doses selected to below 2,000 mg/kg. Mean body weight gain was decreased and clinical signs of toxicity were observed for both rats and mice at 2,000 mg/kg. After 13 weeks, male and female rats exposed at 1,000 mg/kg had gained less weight than had the vehicle controls. In the 2-year studies, doses were 0, 250, and 500 mg/kg for male and female rats and 0, 500, and 1,000 mg/kg for male and female mice. Body weights of high dose male rats were 5%-8% lower than those of the vehicle controls after week 59, and in high dose mice, hyperactivity was observed after dosing from week 4 until the end of the studies. Both observations indicated slight xylenes toxicity, and much higher doses would not likely have been well tolerated.

Dosed male rats had a somewhat higher mortality rate than did the vehicle controls, but the number of gavage-related deaths was also higher in these groups. It is possible that the dosed males resisted gavaging because of the xylenes, but observations on their behavior during gavaging were not recorded. In mice, male vehicle controls had a lower survival at the end of the study than did the dosed groups. The early deaths were thought to be caused by urinary tract infections, and the later deaths were attributed to the debilitating effects of dorsal fibrosarcomas. The morbidity and mortality associated with these conditions may have been exacerbated by group housing. (The NTP now requires individual cages for mice in all studies.)

There were no significant changes in the incidences of neoplastic or nonneoplastic lesions in rats or mice in the current studies which were considered to be related to administration of xylenes (mixed). In a report presenting data from long-term studies on benzene, Maltoni et al. (1985) provided preliminary findings from long-term exposures to several other solvents, including xylenes, in which 500 mg/kg xylenes in olive oil was given by gavage to Sprague-Dawley rats for 2 years. After 2 years, exposure was stopped, and the study was continued without dosing to week 141. All survivors were then killed and examined for effects of xylenes. Although Maltoni et al. reported an increase in the total number of animals with malignant tumors in dosed versus control males (14/40 vs 11/50) and females (22/40 vs 10/50), the absence of study data makes an evaluation of their findings difficult. In contrast, after 104 weeks of exposure in the current NTP studies with F344/N rats, the total number of females with malignant tumors was not significantly increased at 500 mg/kg (16/50) compared with vehicle controls (12/50), and the total number of males with malignant tumors was significantly decreased at 500 mg/kg (19/50) compared with the vehicle controls (32/50) (Appendix A, Table A1), but this decrease in males was probably due to decreased survival of the high dose group relative to that of the vehicle controls. However, a conclusion based on overall proportion of animals with primary tumors (or with malignant tumors) is not considered to be the best approach for detecting potential carcinogenic effects of chemicals (IARC, 1980; Haseman et al., 1986; McConnell et al., 1986).

In contrast to xylenes, long-term benzene exposure has been shown to cause a variety of toxicologic and carcinogenic effects in both sexes of Sprague-Dawley and Wistar rats and Swiss mice (Maltoni et al., 1985) and F344/N rats and B6C3F$_1$ mice (NTP, 1986; Huff et al., 1986). It is apparent that the addition of methyl groups to the benzene molecule reduces the toxic/carcinogenic potential. One explanation for this difference in potential may be related to the capacity of individual hydrocarbons to induce drug-metabolizing enzymes. Pathiratne et al. (1986) investigated the effects on liver metabolism of benzene, toluene, and xylenes in male Sprague-Dawley rats. Benzene was more effective at inducing the conjugation-system enzymes, whereas the dimethylbenzene, xylenes, was more effective at inducing cytochrome P-450-dependent enzymes and the monomethylbenzene, toluene, induced both systems equally well (Pathiratne et al., 1986). Thus, cytochrome P-450 and related enzymes were induced to a greater degree as the number of methyl groups increased (i.e., xylenes > toluene > benzene), whereas the conjugating enzymes were induced as the number of

methyl groups decreased. Although it has been shown that rat liver metabolism is affected by these aromatic solvents, the relationship between differences in metabolism and in carcinogenic potential of benzene and xylenes is not clear.

The results from numerous in vitro and in vivo short-term assays for genotoxicity were overwhelmingly negative. Not only xylenes, but its components, the *meta-*, *ortho-*, and *para-* isomers of xylene and ethylbenzene, as well as their metabolites, the *meta-*, *ortho-*, and *para-* xylenols and methylbenzyl alcohols, were negative in both bacterial and mammalian cell tests for induction of gene mutations. The only positive responses reported, induction of sex-linked recessive lethal mutations in Drosophila by xylenes and SCEs in human lymphocytes in culture by doses of ethylbenzene that delayed cell cycle, were both classified as "weak." Neither of these studies has been replicated. The results of the NTP-sponsored tests for induction of SCEs by ethylbenzene using cultured CHO cells were negative.

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

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of xylenes (mixed) for male or female F344/N rats given 250 or 500 mg/kg or for male or female $B6C3F_1$ mice given 500 or 1,000 mg/kg.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)
Basal cell carcinoma			1 (2%)
Trichoepithelioma	1 (2%)	1 (2%)	
Keratoacanthoma	1 (2%)	3 (6%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		3 (6%)
Lipoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma	1 (2%)		
Tubular cell adenocarcinoma, metastatic		1 (2%)	
Pheochromocytoma, metastatic		2 (4%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	21 (42%)	18 (36%)	11 (22%)
*Subcutaneous tissue	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)		
#Spleen	(45)	(49)	(49)
Sarcoma, NOS	1 (2%)		
Leukemia, mononuclear cell	1 (2%)		
#Thymus	(33)	(38)	(41)
Thymoma, malignant	1 (3%)		
CIRCULATORY SYSTEM			
#Spleen	(45)	(49)	(49)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Neoplastic nodule	3 (6%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	
#Pancreas	(48)	(46)	(49)
Acinar cell adenoma	1 (2%)	2 (4%)	
#Jejunum	(49)	(43)	(45)
Adenocarcinoma, NOS			1 (2%)
#Colon	(47)	(48)	(47)
Adenomatous polyp, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(48)	(50)	(49)
Tubular cell adenoma		1 (2%)	1 (2%)
Tubular cell adenocarcinoma	1 (2%)	1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(45)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(49)	(50)	(45)
Carcinoma, NOS	3 (6%)	1 (2%)	1 (2%)
Adenoma, NOS	22 (45%)	21 (42%)	12 (27%)
#Adrenal	(49)	(50)	(50)
Cortical adenoma	1 (2%)	4 (8%)	1 (2%)
Cortical carcinoma	1 (2%)		
#Adrenal medulla	(49)	(50)	(50)
Pheochromocytoma	18 (37%)	15 (30%)	12 (24%)
Pheochromocytoma, malignant	1 (2%)	3 (6%)	
#Thyroid	(49)	(48)	(48)
Follicular cell adenoma			2 (4%)
Follicular cell carcinoma	1 (2%)	1 (2%)	1 (2%)
C-cell adenoma	5 (10%)	3 (6%)	3 (6%)
C-cell carcinoma	4 (8%)	3 (6%)	1 (2%)
#Parathyroid	(38)	(38)	(46)
Adenoma, NOS		2 (5%)	1 (2%)
#Pancreatic islets	(48)	(46)	(49)
Islet cell adenoma	6 (13%)	1 (2%)	2 (4%)
Islet cell carcinoma		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)	3 (6%)	
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS		2 (4%)	2 (4%)
Adenocarcinoma, NOS	1 (2%)		
#Prostate	(47)	(50)	(47)
Adenoma, NOS	1 (2%)		
#Testis	(50)	(50)	(49)
Interstitial cell tumor	43 (86%)	38 (76%)	41 (84%)
*Scrotum	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(49)
Granular cell tumor, NOS		1 (2%)	
Astrocytoma	1 (2%)		1 (2%)
#Cerebellum	(49)	(50)	(49)
Granular cell tumor, NOS		1 (2%)	
Ependymoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	2 (4%)
Squamous cell carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Epicardium	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Liposarcoma		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	3	8
Moribund sacrifice	7	14	11
Terminal sacrifice	36	25	20
Dosing accident	3	8	11
TUMOR SUMMARY			
Total animals with primary tumors**	49	47	42
Total primary tumors	149	136	105
Total animals with benign tumors	48	45	42
Total benign tumors	105	98	81
Total animals with malignant tumors	32	30	19
Total malignant tumors	41	33	21
Total animals with secondary tumors##	1	3	
Total secondary tumors	1	3	
Total animals with tumors uncertain-- benign or malignant	3	5	2
Total uncertain tumors	3	5	3

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): VEHICLE CONTROL

ANIMAL NUMBER	046	048	007	022	031	034	032	018	017	040	042	019	004	030	001	002	003	005	006	008	009	010	011	012	013
WEEKS ON STUDY	062	064	075	075	075	081	083	084	087	094	094	096	100	102	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Squamous cell papilloma																						X			
Trichoepithelioma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Fibroma																									
Lipoma						X																			
Malignant lymphoma, lymphocytic type																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma				X																					
Trachea	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
Leukemia, mononuclear cell																					X				
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	−	−	+	+	+	−	−	+	−	+	+	+	+	+	+	+	−	−	−	+	−
Thymoma, malignant																	X								
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule														X											
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X																			
Adenoma, NOS					X				X				X	X	X		X	X		X			X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																									
Pheochromocytoma							X	X	X				X		X	X					X	X	X	X	
Pheochromocytoma, malignant																									
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma												X			X							X	X	
C-cell carcinoma																									
Parathyroid	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	+	+
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X						X						X		
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	N	+	N	N	N	N	N	+	+	+	N	+	+	+	N	+	+	+	N	N	N	+
Fibroadenoma												X													
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																		X							
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma										X															
BODY CAVITIES																									
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X				X	X		X	X		X	X	X		X					X			X		

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

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

ANIMAL NUMBER	0014	0015	0016	0020	0021	0023	0024	0025	0026	0027	0028	0029	0033	0035	0036	0037	0038	0039	0041	0043	0044	0045	0047	0049	0050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Trichoepithelioma																						X				1
Keratoacanthoma									X																	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																				X						1
Lipoma																										1
Malignant lymphoma, lymphocytic type		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Sarcoma, NOS																										1
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	46
Thymus	+	+	+	+	+	+	+	+	+	+	−	+	−	+	−	+	+	+	−	−	−	+	−	+	+	33
Thymoma, malignant																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																			X			X				3
Hepatocellular carcinoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma							X																			1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Tubular cell adenocarcinoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																	X							X		3
Adenoma, NOS		X	X			X	X		X		X							X	X@		X		X	X		22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma									X																	1
Cortical carcinoma	X																									1
Pheochromocytoma			X		X				X	X	X			X	X							X				18
Pheochromocytoma, malignant												X														1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																X										1
C-cell adenoma					X																					5
C-cell carcinoma				X		X			X											X						4
Parathyroid	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	+	+	−	−	+	38
Pancreatic islets	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma						X																X			X	6
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	N	+	N	N	N	+	+	+	N	+	+	N	N	N	N	N	N	+	N	N	+	*50
Fibroadenoma		X																								2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Prostate	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	47
Adenoma, NOS									X																	1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
BODY CAVITIES																										
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, metast																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell				X					X	X		X		X				X	X	X		X			X	21

* Animals necropsied

@ Multiple occurrence of morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): LOW DOSE

ANIMAL NUMBER	0023	0043	0195	0155	0006	0122	0055	0011	0222	0088	0550	0111	0338	0334	0330	0339	0444	0141	0331	0044	0185	0332	0166	0472	0002
WEEKS ON STUDY	0029	0444	0535	0556	0688	0688	0711	0722	0722	0755	0811	0833	0844	0855	0866	0866	0877	0900	0933	0955	0955	0997	1000	1022	1044
INTEGUMENTARY SYSTEM																									
Skin	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Trichoepithelioma																					X				
Keratoacanthoma						X																			X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma, metastatic																									
Pheochromocytoma, metastatic			X																						
Trachea	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	−	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	−	+	−	+	+	+	+	−	−	+	+	−	+	+	+	+	−	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma																									
Urinary bladder	−	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS									X		X	X			X	X	X		X	X		X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma									X						X										
Pheochromocytoma																			X	X	X		X		
Pheochromocytoma, malignant			X																						
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma								X																	
C-cell adenoma										X												X			
C-cell carcinoma																									
Parathyroid	+	−	+	−	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	−	−	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma															X										
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	N	N	N	N	+	+	+	+	+	N	+	+	N	+	+	+	N	N	+	N	N
Fibroadenoma																X									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X		X		X	X	X	X	X	X	X		X				X	X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS												X											X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																								X	
Ependymoma				X																					
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Carcinoma, NOS																			X						
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS										X															
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Liposarcoma																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Leukemia, mononuclear cell							X			X	X	X	X			X		X		X	X	X			

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

ANIMAL NUMBER	0003	0007	0009	0110	0113	0117	0120	0121	0124	0125	0126	0127	0128	0129	0133	0135	0136	0137	0140	0141	0142	0145	0146	0148	0149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma											X															1
Trichoepithelioma																										1
Keratoacanthoma						X																				3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma, metastati																					X					1
Pheochromocytoma, metastatic															X											2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma					X																					1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	46
Thymus	+	−	+	+	+	−	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																									X	1
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Acinar cell adenoma										X												X				2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenomatous polyp, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma								X																		1
Tubular cell adenocarcinoma																					X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS					X																					1
Adenoma, NOS		X	X			X			X									X	X	X	X	X	X			21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma		X					X																			4
Pheochromocytoma				X		X	X		X	X			X					X		X	X			X	X	15
Pheochromocytoma, malignant											X				X											3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma																										1
C-cell adenoma																					X					3
C-cell carcinoma				X														X					X			3
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	38
Adenoma, NOS																X	X									2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Islet cell adenoma												X														1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	+	+	N	N	+	+	+	N	+	N	N	N	N	N	+	N	+	N	+	+	N	*50
Fibroadenoma									X				X													3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																					X					2
Ependymoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Liposarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS			X																							1
Leukemia, mononuclear cell	X		X							X		X								X	X			X	X	18

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): HIGH DOSE

ANIMAL NUMBER	0002	0009	0041	0034	0017	0045	0043	0038	0027	0021	0049	0007	0016	0004	0005	0044	0040	0050	0039	0032	0030	0037	0018	0001	0036
WEEKS ON STUDY	027	041	043	044	045	046	047	057	063	075	077	078	080	082	083	083	084	084	086	088	091	096	097	098	098
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Thymus	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	A	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adenocarcinoma, NOS																		X							
Large intestine	+	A	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	A	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	A	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS														X	X									X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																		X	X			X	X		
Thyroid	+	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma															X										
C-cell carcinoma																									
Parathyroid	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	+	N	N	N	+	N	+	+	+	+	N	+	N	N	+	+	N	N	+	N
Testis	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Carcinoma, NOS																				X					
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X				X		X			X		X	X			X
Scrotum, NOS																									
Mesothelioma, NOS														X											

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

ANIMAL NUMBER	023	031	013	048	015	003	006	008	010	011	012	014	019	020	022	024	025	026	028	029	033	035	042	046	047	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	099	099	101	101	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Basal cell carcinoma								X																		1
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma							X		X			X														3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	46
Thymus	+	−	−	+	+	+	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS																			X							1
Adenoma, NOS	X	X		X					X							X	X		X	X	X					12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma						X																				1
Pheochromocytoma				X				X	X			X		X					X		X	X				12
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma												X							X							2
Follicular cell carcinoma																								X		1
C-cell adenoma									X																X	3
C-cell carcinoma											X															1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																							X			1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma		X							X																	2
Islet cell carcinoma	X											X														2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	+	N	N	N	+	+	+	+	N	+	N	+	+	N	N	N	+	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS						X			X																	2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma																									X	1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X																	2
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell												X					X				X			X		11
Scrotum, NOS																										
Mesothelioma, NOS																										1

*Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	Vehicle Control	250 mg/kg	500 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.8%	9.7%	0.0%
Terminal Rates (c)	1/36 (3%)	2/26 (8%)	0/20 (0%)
Week of First Observation	104	68	
Life Table Tests (d)	P=0.534N	P=0.221	P=0.617N
Incidental Tumor Tests (d)	P=0.522N	P=0.259	P=0.617N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.8%	0.0%	15.0%
Terminal Rates (c)	1/36 (3%)	0/26 (0%)	3/20 (15%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.074	P=0.565N	P=0.125
Incidental Tumor Tests (d)	P=0.074	P=0.565N	P=0.125
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	22/50 (44%)	18/50 (36%)	11/50 (22%)
Adjusted Rates (b)	49.4%	48.0%	35.7%
Terminal Rates (c)	14/36 (39%)	8/26 (31%)	4/20 (20%)
Week of First Observation	62	71	75
Life Table Tests (d)	P=0.270N	P=0.487	P=0.286N
Incidental Tumor Tests (d)	P=0.014N	P=0.225N	P=0.022N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.270N	P=0.017N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	23/50 (46%)	18/50 (36%)	11/50 (22%)
Adjusted Rates (b)	51.7%	48.0%	35.7%
Terminal Rates (c)	15/36 (42%)	8/26 (31%)	4/20 (20%)
Week of First Observation	62	71	75
Life Table Tests (d)	P=0.224N	P=0.546	P=0.241N
Incidental Tumor Tests (d)	P=0.009N	P=0.177N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.208N	P=0.010N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/49 (2%)
Adjusted Rates (b)	8.1%	3.8%	5.0%
Terminal Rates (c)	2/36 (6%)	1/26 (4%)	1/20 (5%)
Week of First Observation	102	104	104
Life Table Tests (d)	P=0.382N	P=0.427N	P=0.528N
Incidental Tumor Tests (d)	P=0.302N	P=0.378N	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.207N		
Fisher Exact Test (d)		P=0.309N	P=0.316N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/49 (2%)
Adjusted Rates (b)	8.1%	6.9%	5.0%
Terminal Rates (c)	2/36 (6%)	1/26 (4%)	1/20 (5%)
Week of First Observation	102	95	104
Life Table Tests (d)	P=0.413N	P=0.635N	P=0.528N
Incidental Tumor Tests (d)	P=0.281N	P=0.556N	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.228N		
Fisher Exact Test (d)		P=0.500N	P=0.316N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	22/49 (45%)	21/50 (42%)	12/45 (27%)
Adjusted Rates (b)	54.7%	57.2%	45.2%
Terminal Rates (c)	18/36 (50%)	11/26 (42%)	6/19 (32%)
Week of First Observation	75	72	82
Life Table Tests (d)	P=0.501N	P=0.222	P=0.515N
Incidental Tumor Tests (d)	P=0.070N	P=0.582	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.465N	P=0.052N
Pituitary Gland: Carcinoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	1/45 (2%)
Adjusted Rates (b)	7.7%	3.8%	5.3%
Terminal Rates (c)	2/36 (6%)	1/26 (4%)	1/19 (5%)
Week of First Observation	81	104	104
Life Table Tests (d)	P=0.368N	P=0.408N	P=0.505N
Incidental Tumor Tests (d)	P=0.302N	P=0.330N	P=0.403N
Cochran-Armitage Trend Test (d)	P=0.221N		
Fisher Exact Test (d)		P=0.301N	P=0.341N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	24/49 (49%)	22/50 (44%)	12/45 (27%)
Adjusted Rates (b)	58.2%	60.0%	45.2%
Terminal Rates (c)	19/36 (53%)	12/26 (46%)	6/19 (32%)
Week of First Observation	75	72	82
Life Table Tests (d)	P=0.386N	P=0.261	P=0.384N
Incidental Tumor Tests (d)	P=0.030N	P=0.500N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.384N	P=0.022N
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	2.8%	12.3%	5.0%
Terminal Rates (c)	1/36 (3%)	2/26 (8%)	1/20 (5%)
Week of First Observation	104	72	104
Life Table Tests (d)	P=0.414	P=0.117	P=0.625
Incidental Tumor Tests (d)	P=0.491	P=0.187	P=0.625
Cochran-Armitage Trend Test (d)	P=0.593N		
Fisher Exact Test (d)		P=0.187	P=0.747N
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	5.6%	12.3%	5.0%
Terminal Rates (c)	2/36 (6%)	2/26 (8%)	1/20 (5%)
Week of First Observation	104	72	104
Life Table Tests (d)	P=0.572	P=0.228	P=0.701N
Incidental Tumor Tests (d)	P=0.546N	P=0.323	P=0.701N
Cochran-Armitage Trend Test (d)	P=0.398N		
Fisher Exact Test (d)		P=0.349	P=0.492N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	18/49 (37%)	15/50 (30%)	12/50 (24%)
Adjusted Rates (b)	44.6%	49.6%	45.6%
Terminal Rates (c)	14/36 (39%)	11/26 (42%)	7/20 (35%)
Week of First Observation	83	93	84
Life Table Tests (d)	P=0.400	P=0.424	P=0.467
Incidental Tumor Tests (d)	P=0.274N	P=0.503N	P=0.279N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test (d)		P=0.310N	P=0.123N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.8%	9.6%	0.0%
Terminal Rates (c)	1/36 (3%)	2/26 (8%)	0/20 (0%)
Week of First Observation	104	53	
Life Table Tests (d)	P=0.534N	P=0.221	P=0.617N
Incidental Tumor Tests (d)	P=0.522N	P=0.259	P=0.617N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.316	P=0.495N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	19/49 (39%)	18/50 (36%)	12/50 (24%)
Adjusted Rates (b)	47.1%	57.2%	45.6%
Terminal Rates (c)	15/36 (42%)	13/26 (50%)	7/20 (35%)
Week of First Observation	83	53	84
Life Table Tests (d)	P=0.432	P=0.243	P=0.529
Incidental Tumor Tests (d)	P=0.248N	P=0.475	P=0.226N
Cochran-Armitage Trend Test (d)	P=0.072N		
Fisher Exact Test (d)		P=0.469N	P=0.086N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	1/48 (2%)	3/48 (6%)
Adjusted Rates (b)	2.8%	2.3%	15.0%
Terminal Rates (c)	1/36 (3%)	0/26 (0%)	3/20 (15%)
Week of First Observation	104	72	104
Life Table Tests (d)	P=0.094	P=0.712	P=0.125
Incidental Tumor Tests (d)	P=0.093	P=0.728N	P=0.125
Cochran-Armitage Trend Test (d)	P=0.197		
Fisher Exact Test (d)		P=0.747	P=0.301
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/49 (10%)	3/48 (6%)	3/48 (6%)
Adjusted Rates (b)	13.4%	9.4%	12.5%
Terminal Rates (c)	4/36 (11%)	1/26 (4%)	2/20 (10%)
Week of First Observation	96	75	83
Life Table Tests (d)	P=0.530N	P=0.524N	P=0.642N
Incidental Tumor Tests (d)	P=0.379N	P=0.396N	P=0.507N
Cochran-Armitage Trend Test (d)	P=0.292N		
Fisher Exact Test (d)		P=0.369N	P=0.369N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/49 (8%)	3/48 (6%)	1/48 (2%)
Adjusted Rates (b)	11.1%	11.5%	5.0%
Terminal Rates (c)	4/36 (11%)	3/26 (12%)	1/20 (5%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.333N	P=0.637	P=0.391N
Incidental Tumor Tests (d)	P=0.333N	P=0.637	P=0.391N
Cochran-Armitage Trend Test (d)	P=0.138N		
Fisher Exact Test (d)		P=0.512N	P=0.187N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/49 (18%)	6/48 (13%)	4/48 (8%)
Adjusted Rates (b)	24.2%	20.3%	17.4%
Terminal Rates (c)	8/36 (22%)	4/26 (15%)	3/20 (15%)
Week of First Observation	96	75	83
Life Table Tests (d)	P=0.352N	P=0.533N	P=0.424N
Incidental Tumor Tests (d)	P=0.245N	P=0.434N	P=0.315N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.303N	P=0.124N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	6/48 (13%)	1/46 (2%)	2/49 (4%)
Adjusted Rates (b)	16.4%	4.0%	8.8%
Terminal Rates (c)	5/35 (14%)	1/25 (4%)	1/20 (5%)
Week of First Observation	94	104	99
Life Table Tests (d)	P=0.207N	P=0.128N	P=0.354N
Incidental Tumor Tests (d)	P=0.134N	P=0.110N	P=0.228N
Cochran-Armitage Trend Test (d)	P=0.068N		
Fisher Exact Test (d)		P=0.062N	P=0.127N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	6/48 (13%)	2/46 (4%)	4/49 (8%)
Adjusted Rates (b)	16.4%	6.7%	17.2%
Terminal Rates (c)	5/35 (14%)	1/25 (4%)	2/20 (10%)
Week of First Observation	94	86	99
Life Table Tests (d)	P=0.572N	P=0.255N	P=0.569
Incidental Tumor Tests (d)	P=0.376N	P=0.183N	P=0.507N
Cochran-Armitage Trend Test (d)	P=0.281N		
Fisher Exact Test (d)		P=0.148N	P=0.357N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.3%	10.3%	0.0%
Terminal Rates (c)	1/36 (3%)	2/26 (8%)	0/20 (0%)
Week of First Observation	96	86	
Life Table Tests (d)	P=0.344N	P=0.373	P=0.340N
Incidental Tumor Tests (d)	P=0.221N	P=0.489	P=0.230N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	43/50 (86%)	38/50 (76%)	41/49 (84%)
Adjusted Rates (b)	97.7%	94.8%	100.0%
Terminal Rates (c)	35/36 (97%)	24/26 (92%)	20/20 (100%)
Week of First Observation	75	56	63
Life Table Tests (d)	P=0.001	P=0.132	P<0.001
Incidental Tumor Tests (d)	P=0.028	P=0.559N	P=0.027
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.154N	P=0.483N

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

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, acute necrotizing		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Hyperkeratosis			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Necrosis, fat		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Nasal turbinate	(50)	(50)	(50)
Congestion, NOS			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, acute	1 (2%)	2 (4%)	
Inflammation, interstitial			3 (6%)
Pneumonia, aspiration	1 (2%)		
Bronchopneumonia, acute	1 (2%)		
Inflammation, acute focal		3 (6%)	
Inflammation, acute/chronic	1 (2%)		1 (2%)
Pneumonia, interstitial chronic		2 (4%)	
Inflammation, chronic focal			1 (2%)
Granuloma, NOS	1 (2%)		
Inflammation, granulomatous focal	8 (16%)		2 (4%)
Foreign material, NOS	6 (12%)	7 (14%)	17 (34%)
Hyperplasia, alveolar epithelium		3 (6%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(48)	(50)
Myelofibrosis	1 (2%)	1 (2%)	
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, reticulum cell	1 (2%)		
Hypoplasia, hematopoietic			2 (4%)
#Spleen	(45)	(49)	(49)
Congestion, acute		1 (2%)	
Hemorrhage, chronic			1 (2%)
Depletion, lymphoid	1 (2%)	3 (6%)	1 (2%)
#Splenic red pulp	(45)	(49)	(49)
Fibrosis, focal		2 (4%)	1 (2%)
Fibrosis, multifocal	1 (2%)	1 (2%)	1 (2%)
Fibrosis, diffuse	1 (2%)	1 (2%)	
Pigmentation, NOS	1 (2%)		
Hematopoiesis		1 (2%)	
#Lymph node	(46)	(46)	(46)
Depletion, lymphoid			1 (2%)
#Mandibular lymph node	(46)	(46)	(46)
Dilatation, NOS	1 (2%)		
Angiectasis			1 (2%)
Histiocytosis		1 (2%)	
Plasmacytosis			1 (2%)
#Thoracic lymph node	(46)	(46)	(46)
Hemorrhage	1 (2%)		
#Mediastinal lymph node	(46)	(46)	(46)
Hyperplasia, reticulum cell	1 (2%)		

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(46)	(46)	(46)
Hemorrhage	2 (4%)		
#Thymic lymph node	(46)	(46)	(46)
Hemorrhage		1 (2%)	
Pigmentation, NOS		1 (2%)	
#Thymus	(33)	(38)	(41)
Hemorrhage		1 (3%)	
Depletion, lymphoid		1 (3%)	
CIRCULATORY SYSTEM			
#Brain	(49)	(50)	(49)
Thrombosis, NOS			1 (2%)
#Mandibular lymph node	(46)	(46)	(46)
Lymphangiectasis	1 (2%)		
#Mesenteric lymph node	(46)	(46)	(46)
Lymphangiectasis	1 (2%)	1 (2%)	1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombus, organized	2 (4%)		1 (2%)
Thrombus, mural	1 (2%)	2 (4%)	3 (6%)
Inflammation, chronic diffuse		1 (2%)	
#Myocardium	(50)	(50)	(50)
Mineralization		2 (4%)	
Inflammation, chronic focal	1 (2%)		
Degeneration, NOS	43 (86%)	45 (90%)	48 (96%)
#Myocardium/left atrium	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
#Endocardium	(50)	(50)	(50)
Fibrosis, multifocal		1 (2%)	
*Artery	(50)	(50)	(50)
Perivasculitis		1 (2%)	
#Adrenal cortex	(49)	(50)	(50)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
#Salivary mucous gland	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Degeneration, NOS			1 (2%)
Hyperplasia, focal			1 (2%)
#Liver	(50)	(50)	(49)
Abscess, NOS		1 (2%)	
Inflammation, granulomatous focal	1 (2%)	1 (2%)	
Degeneration, cystic	3 (6%)	1 (2%)	1 (2%)
Necrosis, coagulative	2 (4%)	1 (2%)	4 (8%)
Basophilic cyto change	26 (52%)	15 (30%)	15 (31%)
Focal cellular change	1 (2%)	1 (2%)	
Eosinophilic cyto change	1 (2%)		
Clear cell change		1 (2%)	
Angiectasis		2 (4%)	
Regeneration, NOS	1 (2%)		
Nodular regeneration		1 (2%)	
#Hepatic capsule	(50)	(50)	(49)
Inflammation, fibrinous			1 (2%)
#Liver/centrilobular	(50)	(50)	(49)
Degeneration, NOS		1 (2%)	1 (2%)
Necrosis, focal		2 (4%)	1 (2%)
#Liver/midlobular	(50)	(50)	(49)
Degeneration, NOS			1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver/periportal	(50)	(50)	(49)
Metamorphosis, fatty		1 (2%)	
#Bile duct	(50)	(50)	(49)
Hyperplasia, focal	50 (100%)	49 (98%)	44 (90%)
#Pancreas	(48)	(46)	(49)
Inflammation, acute necrotizing		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
#Pancreatic acinus	(48)	(46)	(49)
Necrosis, focal			1 (2%)
Atrophy, focal	22 (46%)	14 (30%)	9 (18%)
Atrophy, diffuse	2 (4%)		
Hyperplasia, focal	5 (10%)		
#Peripancreatic tissue	(48)	(46)	(49)
Inflammation, chronic focal		1 (2%)	
#Esophagus/muscularis	(49)	(50)	(49)
Inflammation, chronic focal		1 (2%)	
#Periesophageal tissue	(49)	(50)	(49)
Hemorrhage		1 (2%)	
Inflammation, acute focal	1 (2%)		1 (2%)
Foreign material, NOS	1 (2%)		
#Stomach	(47)	(47)	(48)
Ulcer, acute			1 (2%)
Ulcer, chronic		1 (2%)	
#Gastric mucosa	(47)	(47)	(48)
Mineralization		1 (2%)	
Necrosis, focal		2 (4%)	
#Glandular stomach	(47)	(47)	(48)
Mineralization		1 (2%)	1 (2%)
Ulcer, NOS		1 (2%)	1 (2%)
Ulcer, acute		1 (2%)	
Inflammation, acute focal		1 (2%)	
Erosion			2 (4%)
Necrosis, focal		1 (2%)	
#Gastric submucosa	(47)	(47)	(48)
Inflammation, acute diffuse			1 (2%)
#Gastric muscularis	(47)	(47)	(48)
Abscess, chronic		1 (2%)	
#Forestomach	(47)	(47)	(48)
Ulcer, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Ulcer, acute			2 (4%)
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse		1 (2%)	
Ulcer, chronic		1 (2%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Ulcer, perforated			1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, epithelial	1 (2%)	3 (6%)	1 (2%)
Hyperkeratosis			1 (2%)
#Small intestine/serosa	(49)	(43)	(45)
Inflammation, acute/chronic			1 (2%)
#Jejunum	(49)	(43)	(45)
Necrosis, hemorrhagic			1 (2%)
#Jejunal mucosa	(49)	(43)	(45)
Inflammation, acute focal			1 (2%)
#Colon	(47)	(48)	(47)
Parasitism	4 (9%)	3 (6%)	1 (2%)
#Cecum	(47)	(48)	(47)
Ulcer, acute			1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(48)	(50)	(49)
Granuloma, pyogenic	1 (2%)		
Nephropathy	47 (98%)	45 (90%)	46 (94%)
Infarct, healed	1 (2%)		
#Kidney/cortex	(48)	(50)	(49)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, cystic			1 (2%)
Metaplasia, osseous	1 (2%)		
#Kidney/medulla	(48)	(50)	(49)
Inflammation, acute focal		1 (2%)	
#Kidney/tubule	(48)	(50)	(49)
Pigmentation, NOS		2 (4%)	
#Kidney/pelvis	(48)	(50)	(49)
Inflammation, acute focal		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(46)	(46)	(45)
Necrosis, hemorrhagic			1 (2%)
#Urinary bladder/serosa	(46)	(46)	(45)
Inflammation, acute/chronic			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(45)
Ultimobranchial cyst	1 (2%)		
Cyst, NOS	1 (2%)		
#Anterior pituitary	(49)	(50)	(45)
Embryonal duct cyst		1 (2%)	
Cyst, NOS	2 (4%)	1 (2%)	
Necrosis, focal		2 (4%)	1 (2%)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	2 (4%)	3 (6%)	4 (9%)
Hyperplasia, chromophobe cell	2 (4%)		
#Adrenal cortex	(49)	(50)	(50)
Cyst, NOS			1 (2%)
Degeneration, lipoid	6 (12%)	4 (8%)	4 (8%)
Necrosis, focal		1 (2%)	1 (2%)
Focal cellular change	1 (2%)	1 (2%)	
Hyperplasia, focal	9 (18%)	16 (32%)	8 (16%)
#Adrenal medulla	(49)	(50)	(50)
Hyperplasia, focal	6 (12%)	10 (20%)	9 (18%)
#Thyroid	(49)	(48)	(48)
Multilocular cyst	1 (2%)		
Hyperplasia, C-cell	17 (35%)	16 (33%)	14 (29%)
#Parathyroid	(38)	(38)	(46)
Hyperplasia, NOS		2 (5%)	
Hyperplasia, focal			1 (2%)
Hyperplasia, diffuse		1 (3%)	1 (2%)
#Pancreatic islets	(48)	(46)	(49)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Multiple cysts			1 (2%)
Hyperplasia, diffuse			1 (2%)
Hyperplasia, cystic	4 (8%)	11 (22%)	3 (6%)
*Mammary acinus	(50)	(50)	(50)
Hyperplasia, focal			1 (2%)
*Preputial gland	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(47)	(50)	(47)
Multilocular cyst	1 (2%)		
Inflammation, necrotizing			1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, acute diffuse		1 (2%)	
Inflammation, acute necrotizing			1 (2%)
Inflammation, acute/chronic	1 (2%)	2 (4%)	
Inflammation, chronic focal	5 (11%)	1 (2%)	1 (2%)
Inflammation, chronic diffuse	1 (2%)		
Abscess, chronic		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Testis	(50)	(50)	(49)
Necrosis, ischemic			1 (2%)
Hyperplasia, interstitial cell	10 (20%)	13 (26%)	11 (22%)
#Spermatogenic epithelium	(50)	(50)	(49)
Degeneration, NOS	3 (6%)	1 (2%)	4 (8%)
Atrophy, NOS		1 (2%)	
Atrophy, diffuse		7 (14%)	2 (4%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(49)
Hydrocephalus, NOS		1 (2%)	
Inflammation, granulomatous			1 (2%)
Necrosis, hemorrhagic	1 (2%)	1 (2%)	2 (4%)
#Hypothalamus	(49)	(50)	(49)
Atrophy, pressure		2 (4%)	
#Cerebellum	(49)	(50)	(49)
Mineralization	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Mineralization	1 (2%)		
*Eye, anterior chamber	(50)	(50)	(50)
Inflammation, acute diffuse		1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Ulcer, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Ulcer, chronic	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, focal	1 (2%)		
Atrophy, diffuse		1 (2%)	1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
Cataract		1 (2%)	
*Eyelid,	(50)	(50)	(50)
Fibrosis, multifocal	1 (2%)		
*Tarsal gland	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Fibrous osteodystrophy		2 (4%)	
Osteosclerosis			1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		
Foreign material, NOS	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, acute diffuse		1 (2%)	
Inflammation granulomatous focal			1 (2%)
*Mediastinal pleura	(50)	(50)	(50)
Inflammation, acute necrotizing		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute fibrinous		1 (2%)	
Inflammation, acute hemorrhagic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Necrosis, fat		7 (14%)	6 (12%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf			1

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		
Fibrosarcoma		1 (2%)	
Lipoma	1 (2%)		
RESPIRATORY SYSTEM			
None			
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	7 (14%)	12 (24%)	10 (20%)
#Spleen	(50)	(50)	(49)
Leukemia, mononuclear cell			1 (2%)
CIRCULATORY SYSTEM			
#Uterus	(50)	(50)	(50)
Hemangioma		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	2 (4%)	2 (4%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Sarcoma, NOS			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(48)	(49)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(49)	(48)	(49)
Squamous cell carcinoma, invasive	1 (2%)		
Adenoma, NOS	32 (65%)	23 (48%)	31 (63%)
Adenocarcinoma, NOS	1 (2%)	3 (6%)	1 (2%)
#Adrenal	(50)	(49)	(49)
Cortical adenoma	1 (2%)	1 (2%)	2 (4%)
#Adrenal medulla	(50)	(49)	(49)
Pheochromocytoma	2 (4%)	3 (6%)	3 (6%)
Pheochromocytoma, malignant		1 (2%)	
Ganglioneuroma		1 (2%)	
#Thyroid	(50)	(49)	(49)
Follicular cell adenoma	1 (2%)	1 (2%)	
C-cell adenoma	3 (6%)	2 (4%)	5 (10%)
C-cell carcinoma	2 (4%)		
#Parathyroid	(45)	(39)	(40)
Adenoma, NOS		1 (3%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma	1 (2%)		
Islet cell carcinoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			3 (6%)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	14 (28%)	14 (28%)	16 (32%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	1 (2%)
Adenocarcinoma, NOS			2 (4%)
#Uterus	(50)	(50)	(50)
Adenocarcinoma, NOS	2 (4%)		1 (2%)
Fibroma	1 (2%)		
Leiomyoma		1 (2%)	
Endometrial stromal polyp	9 (18%)	13 (26%)	12 (24%)
Endometrial stromal sarcoma	1 (2%)	2 (4%)	1 (2%)
#Cervix uteri	(50)	(50)	(50)
Granular cell tumor, NOS	1 (2%)		
#Ovary	(50)	(50)	(50)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Granular cell tumor, NOS	1 (2%)		
Astrocytoma		1 (2%)	
#Hypothalamus	(50)	(50)	(50)
Adenocarcinoma, NOS, invasive		1 (2%)	
#Medulla oblongata	(50)	(50)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
Adenocarcinoma, NOS, invasive		2 (4%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Squamous cell carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	5	6
Moribund sacrifice	8	10	8
Terminal sacrifice	38	33	35
Dosing accident		1	1
Accidentally killed, NOS		1	
TUMOR SUMMARY			
Total animals with primary tumors**	46	45	46
Total primary tumors	91	87	93
Total animals with benign tumors	41	37	40
Total benign tumors	70	64	74
Total animals with malignant tumors	12	19	16
Total malignant tumors	16	21	17
Total animals with secondary tumors##	1	3	
Total secondary tumors	2	3	
Total animals with tumors uncertain-- benign or malignant	4	2	2
Total uncertain tumors	5	2	2

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): VEHICLE CONTROL

ANIMAL NUMBER	0008	0010	0028	0007	0004	0012	0003	0006	0037	0029	0023	0001	0002	0005	0009	0011	0013	0014	0015	0016	0017	0018	0019	0020	0021
WEEKS ON STUDY	077	078	080	085	086	086	088	089	096	100	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Lipoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive											X														
Adenoma, NOS	X			X				X	X	X	X	X		X		X	X	X	X	X	X	X	X		
Adenocarcinoma, NOS															X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma														X											
C-cell adenoma																									
C-cell carcinoma																				X					
Parathyroid	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	+	+	N	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma													X					X				X	X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS							X				X														
Fibroma					X																				
Endometrial stromal polyp						X																		X	
Endometrial stromal sarcoma		X																							
Granular cell tumor, NOS																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic											X														
Granular cell tumor, NOS																							X		
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS											X														
Zymbal gland	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS						X																			
Squamous cell carcinoma											X														
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell						X		X	X											X					

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

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

ANIMAL NUMBER	0222	0224	0225	0226	0227	0230	0231	0232	0233	0234	0235	0236	0238	0239	0240	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule	X																									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive																										1
Adenoma, NOS	X		X	X			X	X	X		X	X@X			X		X			X	X	X		X		X	32
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																			X	X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma										X								X		X						3
C-cell carcinoma														X												2
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	N	+	N	+	N	+	+	*50
Adenocarcinoma, NOS																				X						1
Fibroadenoma			X	X	X		X			X					X		X					X				14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										2
Fibroma																										1
Endometrial stromal polyp	X						X	X	X			X	X				X									9
Endometrial stromal sarcoma																										1
Granular cell tumor, NOS																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Granular cell tumor, NOS																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																X		X		X						7

* Animals necropsied

@ Multiple occurrence of morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): LOW DOSE

ANIMAL NUMBER	0006	0027	0030	0022	0009	0119	0043	0141	0038	0032	0116	0002	0112	0115	0550	0001	0221	0033	0044	0055	0077	0088	0110	0113
WEEKS ON STUDY	0002	0688	0710	0800	0833	0884	0886	0933	0944	0977	0999	1000	1000	1000	1000	1011	1013	1035	1035	1055	1055	1055	1055	1055
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Keratoacanthoma																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−
Thymus	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	−	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	−	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X						X				X		X	X	X	X		X			X	X
Adenocarcinoma, NOS				X				X				X												
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								
Pheochromocytoma																				X	X			
Pheochromocytoma, malignant										X														
Ganglioneuroma																				X				
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								
C-cell adenoma												X								X				
Parathyroid	+	−	+	+	−	+	+	+	+	+	+	−	+	+	−	−	−	+	+	+	−	+	−	+
Adenoma, NOS																								
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma											X													
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	N	+	+	+	N	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+
Fibroadenoma			X				X				X	X				X	X			X			X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								
Endometrial stromal polyp					X						X									X	X	X		
Endometrial stromal sarcoma									X											X				
Hemangioma																					X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive				X				X				X												
Astrocytoma																								
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X			X	X				X		X	X	X	X						X			

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

ANIMAL NUMBER	0 1 4	0 1 7	0 1 8	0 2 0	0 2 3	0 2 4	0 2 5	0 2 6	0 2 8	0 2 9	0 3 1	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 9	0 4 0	0 4 2	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma							X																			1
Keratoacanthoma																							X			1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	−	+	+	+	+	+	+	+	+	−	−	−	+	+	−	+	−	+	+	+	−	+	+	+	+	39
Thymus	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule													X		X											2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X	X	X	X		X	X	X				X	X				X			X	X			23
Adenocarcinoma, NOS																										3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma							X																			1
Pheochromocytoma																							X			3
Pheochromocytoma, malignant																										1
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma														X												1
C cell adenoma																										2
Parathyroid	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	39
Adenoma, NOS																							X			1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	+	+	+	+	N	+	+	+	+	+	+	N	+	+	N	N	+	N	+	*50
Fibroadenoma					X				X						X		X						X			14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma												X														1
Endometrial stromal polyp		X		X						X		X	X			X								X	X	13
Endometrial stromal sarcoma																										2
Hemangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, invasive																										3
Astrocytoma																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell											X			X						X						12

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): HIGH DOSE

ANIMAL NUMBER	0035	0042	0006	0022	0009	0026	0049	0044	0008	0031	0032	0037	0040	0029	0001	0002	0003	0004	0005	0007	0010	0011	0012	0013	0014
WEEKS ON STUDY	039	071	078	084	086	091	093	095	096	096	100	100	100	101	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS				X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X		X			X	X	X	X	X	X	X			X	X	X	X	X	X		
Adenocarcinoma, NOS								X																	
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma					X																				
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X			X													X					
Parathyroid	+	+	−	+	−	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Fibroadenoma					X	X				X		X		X	X			X		X		X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, NOS																									X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp						X	X			X						X	X		X	X				X	
Endometrial stromal sarcoma																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X				X	X		X								X			X					

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

ANIMAL NUMBER	0151	0161	0171	0181	0191	0201	0211	0231	0241	0251	0271	0281	0301	0331	0341	0361	0381	0391	0411	0431	0451	0461	0471	0481	0501	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma				X																						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell			X																							1
Lymph nodes	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X																			2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X		X					X		X	X	X	X	X	X	X	X	X	X		X	X		X	31
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma															X											2
Pheochromocytoma													X	X												3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C cell adenoma				X																			X			5
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	N	*50
Adenoma, NOS												X		X												3
Fibroadenoma	X	X		X				X								X			X	X						16
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																				X						1
Adenocarcinoma, NOS					X																					2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																					X					1
Endometrial stromal polyp	X				X												X				X					12
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell				X	X					X												X				10

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	Vehicle Control	250 mg/kg	500 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	7/50 (14%)	12/50 (24%)	11/50 (22%)
Adjusted Rates (b)	16.3%	27.9%	26.4%
Terminal Rates (c)	4/39 (10%)	4/33 (12%)	7/36 (19%)
Week of First Observation	86	68	71
Life Table Tests (d)	P=0.185	P=0.127	P=0.203
Incidental Tumor Tests (d)	P=0.204	P=0.269	P=0.209
Cochran-Armitage Trend Test (d)	P=0.191		
Fisher Exact Test (d)		P=0.154	P=0.218
Pituitary Gland: Adenoma			
Overall Rates (a)	32/49 (65%)	23/48 (48%)	31/49 (63%)
Adjusted Rates (b)	71.0%	59.9%	70.4%
Terminal Rates (c)	26/39 (67%)	17/32 (53%)	23/36 (64%)
Week of First Observation	77	71	84
Life Table Tests (d)	P=0.464	P=0.265N	P=0.495
Incidental Tumor Tests (d)	P=0.429N	P=0.055N	P=0.432N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.064N	P=0.500N
Pituitary Gland: Adenocarcinoma			
Overall Rates (a)	1/49 (2%)	3/48 (6%)	1/49 (2%)
Adjusted Rates (b)	2.6%	6.9%	2.3%
Terminal Rates (c)	1/39 (3%)	0/32 (0%)	0/36 (0%)
Week of First Observation	104	80	95
Life Table Tests (d)	P=0.604	P=0.289	P=0.754
Incidental Tumor Tests (d)	P=0.499N	P=0.440	P=0.669N
Cochran-Armitage Trend Test (d)	P=0.609		
Fisher Exact Test (d)		P=0.301	P=0.753
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	33/49 (67%)	26/48 (54%)	32/49 (65%)
Adjusted Rates (b)	73.2%	62.7%	71.1%
Terminal Rates (c)	27/39 (69%)	17/32 (53%)	23/36 (64%)
Week of First Observation	77	71	84
Life Table Tests (d)	P=0.465	P=0.411N	P=0.493
Incidental Tumor Tests (d)	P=0.386N	P=0.089N	P=0.395N
Cochran-Armitage Trend Test (d)	P=0.458N		
Fisher Exact Test (d)		P=0.131N	P=0.500N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	3/49 (6%)
Adjusted Rates (b)	5.1%	9.1%	7.6%
Terminal Rates (c)	2/39 (5%)	3/33 (9%)	2/36 (6%)
Week of First Observation	104	104	86
Life Table Tests (d)	P=0.381	P=0.424	P=0.471
Incidental Tumor Tests (d)	P=0.340	P=0.424	P=0.410
Cochran-Armitage Trend Test (d)	P=0.403		
Fisher Exact Test (d)		P=0.490	P=0.490
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	4/49 (8%)	3/49 (6%)
Adjusted Rates (b)	5.1%	11.3%	7.6%
Terminal Rates (c)	2/39 (5%)	3/33 (9%)	2/36 (6%)
Week of First Observation	104	97	86
Life Table Tests (d)	P=0.386	P=0.276	P=0.471
Incidental Tumor Tests (d)	P=0.384	P=0.353	P=0.410
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.329	P=0.490

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	5/49 (10%)
Adjusted Rates (b)	7.7%	5.5%	12.3%
Terminal Rates (c)	3/39 (8%)	1/33 (3%)	3/36 (8%)
Week of First Observation	104	100	84
Life Table Tests (d)	P=0.256	P=0.565N	P=0.329
Incidental Tumor Tests (d)	P=0.277	P=0.462N	P=0.339
Cochran-Armitage Trend Test (d)	P=0.265		
Fisher Exact Test (d)		P=0.510N	P=0.346
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	2/49 (4%)	5/49 (10%)
Adjusted Rates (b)	12.8%	5.5%	12.3%
Terminal Rates (c)	5/39 (13%)	1/33 (3%)	3/36 (8%)
Week of First Observation	104	100	84
Life Table Tests (d)	P=0.537	P=0.282N	P=0.592
Incidental Tumor Tests (d)	P=0.570	P=0.207N	P=0.606
Cochran-Armitage Trend Test (d)	P=0.561		
Fisher Exact Test (d)		P=0.226N	P=0.617
Mammary Gland: Fibroadenoma			
Overall Rates (a)	14/50 (28%)	14/50 (28%)	16/50 (32%)
Adjusted Rates (b)	35.9%	35.1%	38.5%
Terminal Rates (c)	14/39 (36%)	8/33 (24%)	11/36 (31%)
Week of First Observation	104	71	86
Life Table Tests (d)	P=0.302	P=0.410	P=0.333
Incidental Tumor Tests (d)	P=0.375	P=0.579N	P=0.386
Cochran-Armitage Trend Test (d)	P=0.371		
Fisher Exact Test (d)		P=0.588	P=0.414
Mammary Gland: Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.3%
Terminal Rates (c)	0/39 (0%)	0/33 (0%)	3/36 (8%)
Week of First Observation			104
Life Table Tests (d)	P=0.035	(e)	P=0.107
Incidental Tumor Tests (d)	P=0.035	(e)	P=0.107
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(e)	P=0.121
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	14/50 (28%)	14/50 (28%)	18/50 (36%)
Adjusted Rates (b)	35.9%	35.1%	43.4%
Terminal Rates (c)	14/39 (36%)	8/33 (24%)	13/36 (36%)
Week of First Observation	104	71	86
Life Table Tests (d)	P=0.176	P=0.410	P=0.194
Incidental Tumor Tests (d)	P=0.223	P=0.579N	P=0.230
Cochran-Armitage Trend Test (d)	P=0.224		
Fisher Exact Test (d)		P=0.588	P=0.260
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.6%	0.0%	8.3%
Terminal Rates (c)	1/39 (3%)	0/33 (0%)	3/36 (8%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.163	P=0.533N	P=0.277
Incidental Tumor Tests (d)	P=0.163	P=0.533N	P=0.277
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Clitoral Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5.1%	3.0%	8.3%
Terminal Rates (c)	2/39 (5%)	1/33 (3%)	3/36 (8%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.369	P=0.558N	P=0.463
Incidental Tumor Tests (d)	P=0.369	P=0.558N	P=0.463
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	13/50 (26%)	12/50 (24%)
Adjusted Rates (b)	22.2%	36.4%	30.0%
Terminal Rates (c)	8/39 (21%)	11/33 (33%)	9/36 (25%)
Week of First Observation	86	83	91
Life Table Tests (d)	P=0.225	P=0.131	P=0.264
Incidental Tumor Tests (d)	P=0.217	P=0.137	P=0.273
Cochran-Armitage Trend Test (d)	P=0.275		
Fisher Exact Test (d)		P=0.235	P=0.312
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	10/50 (20%)	14/50 (28%)	13/50 (26%)
Adjusted Rates (b)	23.8%	37.9%	32.6%
Terminal Rates (c)	8/39 (21%)	11/33 (33%)	10/36 (28%)
Week of First Observation	78	83	91
Life Table Tests (d)	P=0.233	P=0.144	P=0.269
Incidental Tumor Tests (d)	P=0.241	P=0.179	P=0.279
Cochran-Armitage Trend Test (d)	P=0.281		
Fisher Exact Test (d)		P=0.241	P=0.317

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. N indicates a negative trend or lower incidence in a dosed group.
(e) No P value is reported because no tumors were observed in the 250 mg/kg and vehicle control groups.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
Abscess, chronic		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
Necrosis, fat			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Congestion, NOS	2 (4%)		
Congestion, acute	1 (2%)		2 (4%)
Congestion, acute passive	1 (2%)		
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, interstitial	1 (2%)		1 (2%)
Pneumonia, aspiration		1 (2%)	
Pneumonia, interstitial chronic	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Foreign material, NOS	3 (6%)	6 (12%)	4 (8%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Myelofibrosis		1 (2%)	
Hyperplasia, hematopoietic	1 (2%)		
Hyperplasia, granulocytic			1 (2%)
Hyperplasia, reticulum cell	1 (2%)	2 (4%)	1 (2%)
#Splenic red pulp	(50)	(50)	(49)
Fibrosis, focal			1 (2%)
Pigmentation, NOS	1 (2%)		
Hemosiderosis			1 (2%)
Hematopoiesis	3 (6%)	1 (2%)	1 (2%)
#Thymus	(42)	(42)	(46)
Cyst, NOS		1 (2%)	
CIRCULATORY SYSTEM			
*Thoracic cavity	(50)	(50)	(50)
Perivasculitis			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Mesenteric lymph node	(47)	(39)	(45)
Lymphangiectasis			1 (2%)
#Base of heart	(50)	(50)	(50)
Perivasculitis			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombus, mural		1 (2%)	
#Myocardium	(50)	(50)	(50)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Degeneration, NOS	35 (70%)	39 (78%)	44 (88%)
Necrosis, focal		1 (2%)	
Hyperplasia, NOS		1 (2%)	

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(48)
Inflammation, acute focal	1 (2%)		
Atrophy, focal		1 (2%)	
Atrophy, diffuse	1 (2%)		
Dysplasia, NOS		1 (2%)	
#Parotid duct	(50)	(50)	(48)
Hyperplasia, epithelial		1 (2%)	
#Liver	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Inflammation, granulomatous focal	13 (26%)	11 (22%)	6 (12%)
Cholangiofibrosis		2 (4%)	
Cytoplasmic change, NOS			1 (2%)
Basophilic cytoplasmic change	39 (78%)	35 (70%)	35 (70%)
Focal cellular change	2 (4%)		1 (2%)
Angiectasis	1 (2%)	1 (2%)	5 (10%)
Regeneration, NOS	1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, focal		1 (2%)	1 (2%)
Necrosis, diffuse	2 (4%)	1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)
Inflammation, granulomatous focal	1 (2%)		
Degeneration, NOS	1 (2%)		
Necrosis, focal	2 (4%)	2 (4%)	1 (2%)
Necrosis, diffuse		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	2 (4%)
Nodular regeneration		1 (2%)	
#Bile duct	(50)	(50)	(50)
Hyperplasia, focal	6 (12%)	8 (16%)	5 (10%)
#Pancreatic acinus	(50)	(50)	(50)
Necrosis, focal	1 (2%)		
Atrophy, focal	14 (28%)	9 (18%)	4 (8%)
Atrophy, diffuse	2 (4%)		1 (2%)
Hyperplasia, focal		1 (2%)	
#Esophagus	(50)	(50)	(50)
Diverticulum		1 (2%)	
#Gastric submucosa	(49)	(49)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic		1 (2%)	
#Gastric serosa	(49)	(49)	(50)
Inflammation, acute		1 (2%)	
#Forestomach	(49)	(49)	(50)
Ulcer, NOS		1 (2%)	
Ulcer, acute			3 (6%)
#Colon	(49)	(48)	(49)
Parasitism		1 (2%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)		
Nephropathy	21 (42%)	22 (44%)	29 (59%)
#Kidney/tubule	(50)	(50)	(49)
Dilatation, NOS	1 (2%)		
Inflammation, acute focal		1 (2%)	
#Kidney/pelvis	(50)	(50)	(49)
Mineralization	2 (4%)		1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder	(49)	(50)	(49)
Necrosis, hemorrhagic			1 (2%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	
#Urinary bladder/submucosa	(49)	(50)	(49)
Mineralization		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(48)	(49)
Cyst, NOS		5 (10%)	
Multiple cysts	1 (2%)	4 (8%)	1 (2%)
Hemorrhagic cyst	2 (4%)		
Necrosis, focal			1 (2%)
Necrosis, hemorrhagic		1 (2%)	
Hemosiderosis	1 (2%)		
Cell size alteration			1 (2%)
Hyperplasia, focal	2 (4%)	8 (17%)	2 (4%)
Angiectasis		3 (6%)	1 (2%)
#Adrenal	(50)	(49)	(49)
Accessory structure			1 (2%)
Angiectasis	1 (2%)		
#Adrenal cortex	(50)	(49)	(49)
Degeneration, lipoid	8 (16%)	5 (10%)	5 (10%)
Necrosis, focal	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	
Cell size alteration	1 (2%)	1 (2%)	5 (10%)
Hypertrophy, focal			1 (2%)
Hyperplasia, epithelial			1 (2%)
Hyperplasia, focal	20 (40%)	11 (22%)	10 (20%)
#Adrenal medulla	(50)	(49)	(49)
Necrosis, diffuse	1 (2%)		
Hyperplasia, focal	6 (12%)	3 (6%)	4 (8%)
#Thyroid	(50)	(49)	(49)
Follicular cyst, NOS	1 (2%)		
Hyperplasia, C-cell	27 (54%)	24 (49%)	26 (53%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Multiple cysts	1 (2%)		1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, diffuse	1 (2%)		4 (8%)
Hyperplasia, cystic	19 (38%)	17 (34%)	21 (42%)
Hyperplasia, adenomatous	1 (2%)		
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)		
Cyst, NOS	1 (2%)		
Cystic ducts		1 (2%)	
#Uterus	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	2 (4%)	5 (10%)
#Cervix uteri	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	
Multiple cysts			1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Multiple cysts	1 (2%)		
Inflammation, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, epithelial	1 (2%)		
Metaplasia, squamous			1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Endometrial gland	(50)	(50)	(50)
Multiple cysts	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, focal		1 (2%)	
#Ovary	(50)	(50)	(50)
Follicular cyst, NOS	2 (4%)		3 (6%)
Parovarian cyst	6 (12%)	2 (4%)	3 (6%)
#Ovary/follicle	(50)	(50)	(50)
Multiple cysts		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hydrocephalus, internal	1 (2%)		1 (2%)
#Hippocampus	(50)	(50)	(50)
Necrosis, focal		1 (2%)	
#Hypothalamus	(50)	(50)	(50)
Atrophy, pressure	4 (8%)	3 (6%)	5 (10%)
#Cerebellum	(50)	(50)	(50)
Mineralization		1 (2%)	
#Medulla oblongata	(50)	(50)	(50)
Necrosis, hemorrhagic		1 (2%)	1 (2%)
Atrophy, pressure	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye, anterior chamber	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, focal		1 (2%)	1 (2%)
Atrophy, diffuse	2 (4%)	3 (6%)	2 (4%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)	4 (8%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*Cortex of bone	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, diffuse	2 (4%)	1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign material, NOS	1 (2%)		
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat			1 (2%)
*Mesentery	(50)	(50)	(50)
Necrosis, fat	1 (2%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*Skin	(48)	(50)	(50)
Squamous cell papilloma	1 (2%)		
*Subcutaneous tissue	(48)	(50)	(50)
Fibroma	1 (2%)	1 (2%)	2 (4%)
Fibrosarcoma	13 (27%)	10 (20%)	8 (16%)
Fibrosarcoma, invasive			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(48)	(50)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	2 (4%)	3 (6%)
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	2 (4%)
Pheochromocytoma, metastatic			1 (2%)
Fibrosarcoma, metastatic	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(48)	(50)	(50)
Malignant lymphoma, lymphocytic type		2 (4%)	1 (2%)
Malignant lymphoma, histiocytic type	3 (6%)		
Malignant lymphoma, mixed type	3 (6%)	4 (8%)	4 (8%)
#Peyer's patch	(38)	(41)	(44)
Malignant lymphoma, mixed type	1 (3%)		
CIRCULATORY SYSTEM			
*Multiple organs	(48)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Myocardium	(48)	(50)	(50)
Hemangioma	1 (2%)		
#Liver	(48)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
#Pancreas	(46)	(49)	(48)
Hemangiosarcoma, invasive		1 (2%)	
#Testis	(48)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(48)	(50)	(50)
Hepatocellular adenoma	9 (19%)	8 (16%)	8 (16%)
Hepatocellular carcinoma	10 (21%)	6 (12%)	10 (20%)
#Forestomach	(45)	(47)	(47)
Squamous cell papilloma	2 (4%)	1 (2%)	1 (2%)
URINARY SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary intermedia	(40)	(46)	(49)
Adenoma, NOS		1 (2%)	
#Adrenal	(48)	(50)	(49)
Cortical adenoma		1 (2%)	
#Adrenal/capsule	(48)	(50)	(49)
Adenoma, NOS	5 (10%)	2 (4%)	2 (4%)
#Adrenal medulla	(48)	(50)	(49)
Pheochromocytoma		3 (6%)	2 (4%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(46)	(48)	(48)
Follicular cell adenoma		1 (2%)	3 (6%)
C-cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Preputial gland	(48)	(50)	(50)
Carcinoma, NOS	1 (2%)		
#Testis	(48)	(50)	(50)
Interstitial cell tumor			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(48)	(50)	(50)
Papillary adenoma		2 (4%)	
Papillary adenocarcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(48)	(50)	(50)
Sarcoma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(48)	(50)	(50)
Fibrosarcoma, metastatic	1 (2%)		2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	14	10	6
Moribund sacrifice	6	5	5
Terminal sacrifice	27	35	36
Dosing accident	1		3
Animal missing	2		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	36	37	33
Total primary tumors	56	49	51
Total animals with benign tumors	17	20	19
Total benign tumors	21	24	24
Total animals with malignant tumors	26	24	23
Total malignant tumors	35	25	27
Total animals with secondary tumors##	4	3	7
Total secondary tumors	4	3	8

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): VEHICLE CONTROL

ANIMAL NUMBER	00006	00008	00107	00223	00244	00330	00344	00299	00505	00841	00921	00925	00904	00917	00945	00909	00946	00935	00932	01015	00939	00942	00101	00002	00003
WEEKS ON STUDY	01616	01618	01707	05010	05544	06686	07979	08080	08282	08282	08484	08486	08886	08886	08686	08787	09292	09393	09898	09909	10313	10403	10403	10404	10404
INTEGUMENTARY SYSTEM																									
Skin	M	M	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	M	M	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma									X			X	X		X	X	X	X	X		X	X		X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X							X								
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma																								X	
Fibrosarcoma, metastatic																			X						
Trachea	M	M	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	M	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Lymph nodes	M	M	+	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+	+
Thymus	M	M	−	−	+	−	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	+
CIRCULATORY SYSTEM																									
Heart	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
DIGESTIVE SYSTEM																									
Salivary gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Liver	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X											X	
Hepatocellular carcinoma								X	X	X			X			X			X					X	X
Hemangiosarcoma																									
Bile duct	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	M	M	N	+	N	N	N	N	N	+	+	N	+	N	N	N	N	N	+	+	N	N	N	+	+
Pancreas	M	M	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	M	M	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Squamous cell papilloma																			X						
Small intestine	M	M	+	+	+	−	−	−	−	+	+	−	+	−	+	−	+	+	+	+	−	−	−	+	+
Malignant lymphoma, mixed type																									
Large intestine	M	M	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	−	−	+	−	+	+
URINARY SYSTEM																									
Kidney	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	M	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	M	M	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−	
Adrenal	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma, NOS																				X		X			
Thyroid	M	M	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid	M	M	+	−	−	−	−	+	−	−	+	+	+	−	+	+	+	+	−	−	−	+	+	−	
REPRODUCTIVE SYSTEM																									
Mammary gland	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenocarcinoma																									
BODY CAVITIES																									
Peritoneum	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic																X									
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									

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

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

ANIMAL NUMBER	007	011	012	013	014	016	018	019	020	022	026	027	028	031	033	036	037	038	040	043	044	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Squamous cell papilloma																			X							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Fibroma													X													1
Fibrosarcoma																		X			X					13
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma														X												2
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	41
Thymus	–	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	–	+	+	–	–	+	+	20
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma	X																									1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma			X		X	X		X	X			X		X												9
Hepatocellular carcinoma																			X				X			10
Hemangiosarcoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma	X																									2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Malignant lymphoma, mixed type		X																								1
Large intestine	+	–	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	37
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	+	+	–	+	+	+	40
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X	X														X										5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	–	–	–	+	+	+	+	+	+	–	–	+	+	+	–	+	+	+	+	–	+	–	+	–	–	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Carcinoma, NOS					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Papillary adenocarcinoma																									X	1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Sarcoma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Fibrosarcoma, metastatic																										1
Malignant lymphoma, histiocytic type										X							X								X	3
Malignant lymphoma, mixed type			X	X																	X					3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): LOW DOSE

ANIMAL NUMBER	0501	0511	0737	0002	0020	0335	0411	0466	0488	0334	0433	0518	0400	0004	0224	0001	0033	0055	0066	0077	0088	0099	0110	0112	0113
WEEKS ON STUDY	0119	0224	0379	0800	0800	0822	0844	0844	0891	0997	0997	0998	0999	1000	1003	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma				X			X		X	X	X		X		X	X			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic								X																	
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	+	−	−	−	−	−	−	+	+	+	−	+	+	+	+	−	+	−	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X									X	X	
Hepatocellular carcinoma				X		X		X												X					
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	N	+	N	N	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, invasive																									
Esophagus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Small intestine	−	+	+	−	+	−	+	−	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	−	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Adenoma, NOS										X															
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X															X							
Cortical adenoma																									
Pheochromocytoma										X						X				X					
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																X									
Parathyroid	+	−	−	+	−	−	+	−	−	−	−	−	−	+	+	+	+	+	+	+	−	−	+	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type												X										X			

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

ANIMAL NUMBER	0 1 4	0 1 5	0 1 6	0 1 7	0 1 9	0 2 1	0 2 2	0 2 3	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 6	0 3 8	0 3 9	0 4 2	0 4 4	0 4 5	0 4 7	0 4 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																								X		1
Fibrosarcoma															X											10
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic	X																									2
Alveolar/bronchiolar adenoma						X														X	X					3
Alveolar/bronchiolar carcinoma																X			X							2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	44
Thymus	−	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	−	+	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X									X		X		X											X	8
Hepatocellular carcinoma	X																				X					6
Hemangiosarcoma						X																				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, invasive						X																				1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	41
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										2
Cortical adenoma																									X	1
Pheochromocytoma																										3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma									X																	1
C-cell adenoma																										1
Parathyroid	−	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	−	+	+	−	+	+	+	+	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																			X				X			2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type		X			X																					2
Malignant lymphoma, mixed type				X							X															4

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): HIGH DOSE

ANIMAL NUMBER	033	007	039	036	038	026	041	011	013	040	005	012	002	028	001	003	004	006	008	009	010	014	015	016	017
WEEKS ON STUDY	010	012	014	018	030	041	060	080	080	087	097	097	099	103	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma							X			X	X		X			X	X								
Fibrosarcoma, invasive																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic												X													
Alveolar/bronchiolar adenoma										X									X			X			
Alveolar/bronchiolar carcinoma																								X	
Pheochromocytoma, metastatic																									
Fibrosarcoma, metastatic							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymus	+	+	+	+	−	−	−	+	−	−	−	−	−	−	+	+	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma									X			X	X	X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	N	N	+	+	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	−	+	−	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Pheochromocytoma																				X					
Pheochromocytoma, malignant																									
Thyroid	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
Parathyroid	+	−	−	−	−	−	−	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Hemangioma															X										
Prostate	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic													X												
Hemangiosarcoma																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																						X			

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

ANIMAL NUMBER	018	019	020	021	022	023	024	025	027	029	030	031	032	034	035	037	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																							X		X	2
Fibrosarcoma	X				X																					6
Fibrosarcoma, invasive	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic					X																			X		3
Alveolar/bronchiolar adenoma										X																4
Alveolar/bronchiolar carcinoma															X											2
Pheochromocytoma, metastatic																	X									1
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymus	−	+	−	−	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X				X		X							X							X		X	X	X	8
Hepatocellular carcinoma					X									X			X		X		X		X			10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS											X															2
Pheochromocytoma																								X		2
Pheochromocytoma, malignant																	X									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma					X	X																				3
Parathyroid	+	−	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	33
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor										X																1
Hemangioma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic	X																									2
Hemangiosarcoma												X														1
Malignant lymphoma, lymphocytic type																	X									1
Malignant lymphoma, mixed type		X	X																			X				4

[a] Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	13/48 (27%)	10/50 (20%)	8/50 (16%)
Adjusted Rates (b)	33.4%	23.1%	19.5%
Terminal Rates (c)	3/28 (11%)	3/35 (9%)	4/36 (11%)
Week of First Observation	82	80	60
Life Table Tests (d)	P=0.078N	P=0.194N	P=0.098N
Incidental Tumor Tests (d)	P=0.442N	P=0.346N	P=0.514N
Cochran-Armitage Trend Test (d)	P=0.111N		
Fisher Exact Test (d)		P=0.278N	P=0.138N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	14/48 (29%)	11/50 (22%)	10/50 (20%)
Adjusted Rates (b)	36.1%	25.5%	24.6%
Terminal Rates (c)	4/28 (14%)	4/35 (11%)	6/36 (17%)
Week of First Observation	82	80	60
Life Table Tests (d)	P=0.114N	P=0.190N	P=0.137N
Incidental Tumor Tests (d)	P=0.519N	P=0.332N	P=0.579N
Cochran-Armitage Trend Test (d)	P=0.172N		
Fisher Exact Test (d)		P=0.280N	P=0.206N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/48 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	6.7%	8.6%	10.6%
Terminal Rates (c)	1/28 (4%)	3/35 (9%)	3/36 (8%)
Week of First Observation	99	104	87
Life Table Tests (d)	P=0.363	P=0.599	P=0.447
Incidental Tumor Tests (d)	P=0.275	P=0.597	P=0.306
Cochran-Armitage Trend Test (d)	P=0.280		
Fisher Exact Test (d)		P=0.520	P=0.359
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	10.1%	14.3%	16.0%
Terminal Rates (c)	2/28 (7%)	5/35 (14%)	5/36 (14%)
Week of First Observation	99	104	87
Life Table Tests (d)	P=0.310	P=0.482	P=0.371
Incidental Tumor Tests (d)	P=0.241	P=0.481	P=0.260
Cochran-Armitage Trend Test (d)	P=0.213		
Fisher Exact Test (d)		P=0.381	P=0.264
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/48 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	10.7%	0.0%	0.0%
Terminal Rates (c)	3/28 (11%)	0/35 (0%)	0/36 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.023N	P=0.084N	P=0.080N
Incidental Tumor Tests (d)	P=0.023N	P=0.084N	P=0.080N
Cochran-Armitage Trend Test (d)	P=0.034N		
Fisher Exact Test (d)		P=0.114N	P=0.114N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/48 (8%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	14.3%	10.9%	11.1%
Terminal Rates (c)	4/28 (14%)	3/35 (9%)	4/36 (11%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.433N	P=0.518N	P=0.500N
Incidental Tumor Tests (d)	P=0.451N	P=0.519N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.550N		
Fisher Exact Test (d)		P=0.619N	P=0.619N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/48 (15%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	25.0%	16.5%	13.9%
Terminal Rates (c)	7/28 (25%)	5/35 (14%)	5/36 (14%)
Week of First Observation	104	98	104
Life Table Tests (d)	P=0.174N	P=0.331N	P=0.212N
Incidental Tumor Tests (d)	P=0.184N	P=0.332N	P=0.212N
Cochran-Armitage Trend Test (d)	P=0.295N		
Fisher Exact Test (d)		P=0.468N	P=0.351N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/48 (19%)	8/50 (16%)	8/50 (16%)
Adjusted Rates (b)	30.5%	22.2%	22.2%
Terminal Rates (c)	8/28 (29%)	7/35 (20%)	8/36 (22%)
Week of First Observation	86	100	104
Life Table Tests (d)	P=0.246N	P=0.310N	P=0.286N
Incidental Tumor Tests (d)	P=0.295N	P=0.338N	P=0.344N
Cochran-Armitage Trend Test (d)	P=0.411N		
Fisher Exact Test (d)		P=0.463N	P=0.463N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/48 (21%)	6/50 (12%)	10/50 (20%)
Adjusted Rates (b)	27.1%	14.5%	24.8%
Terminal Rates (c)	4/28 (14%)	3/35 (9%)	6/36 (17%)
Week of First Observation	80	80	80
Life Table Tests (d)	P=0.412N	P=0.137N	P=0.429N
Incidental Tumor Tests (d)	P=0.268	P=0.271N	P=0.329
Cochran-Armitage Trend Test (d)	P=0.516N		
Fisher Exact Test (d)		P=0.182N	P=0.558N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/48 (38%)	13/50 (26%)	14/50 (28%)
Adjusted Rates (b)	49.7%	32.4%	34.8%
Terminal Rates (c)	11/28 (39%)	9/35 (26%)	10/36 (28%)
Week of First Observation	80	80	80
Life Table Tests (d)	P=0.093N	P=0.083N	P=0.108N
Incidental Tumor Tests (d)	P=0.339N	P=0.162N	P=0.394N
Cochran-Armitage Trend Test (d)	P=0.183N		
Fisher Exact Test (d)		P=0.157N	P=0.216N
Adrenal Gland: Adenoma			
Overall Rates (a)	5/48 (10%)	2/50 (4%)	2/49 (4%)
Adjusted Rates (b)	17.1%	4.9%	5.6%
Terminal Rates (c)	4/28 (14%)	1/35 (3%)	2/36 (6%)
Week of First Observation	99	79	104
Life Table Tests (d)	P=0.091N	P=0.147N	P=0.130N
Incidental Tumor Tests (d)	P=0.128N	P=0.172N	P=0.149N
Cochran-Armitage Trend Test (d)	P=0.139N		
Fisher Exact Test (d)		P=0.201N	P=0.209N
Adrenal Gland: Adenoma or Cortical Adenoma			
Overall Rates (a)	5/48 (10%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	17.1%	7.7%	5.6%
Terminal Rates (c)	4/28 (14%)	2/35 (6%)	2/36 (6%)
Week of First Observation	99	79	104
Life Table Tests (d)	P=0.096N	P=0.253N	P=0.130N
Incidental Tumor Tests (d)	P=0.133N	P=0.286N	P=0.149N
Cochran-Armitage Trend Test (d)	P=0.150N		
Fisher Exact Test (d)		P=0.335N	P=0.209N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/48 (0%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	0.0%	8.0%	5.6%
Terminal Rates (c)	0/28 (0%)	2/35 (6%)	2/36 (6%)
Week of First Observation		97	104
Life Table Tests (d)	P=0.265	P=0.167	P=0.295
Incidental Tumor Tests (d)	P=0.239	P=0.162	P=0.295
Cochran-Armitage Trend Test (d)	P=0.206		
Fisher Exact Test (d)		P=0.129	P=0.253
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	0/48 (0%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	0.0%	8.0%	8.3%
Terminal Rates (c)	0/28 (0%)	2/35 (6%)	3/36 (8%)
Week of First Observation		97	104
Life Table Tests (d)	P=0.146	P=0.167	P=0.168
Incidental Tumor Tests (d)	P=0.129	P=0.162	P=0.168
Cochran-Armitage Trend Test (d)	P=0.103		
Fisher Exact Test (d)		P=0.129	P=0.125
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/46 (0%)	1/48 (2%)	3/48 (6%)
Adjusted Rates (b)	0.0%	2.9%	8.3%
Terminal Rates (c)	0/28 (0%)	1/35 (3%)	3/36 (8%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.084	P=0.545	P=0.168
Incidental Tumor Tests (d)	P=0.084	P=0.545	P=0.168
Cochran-Armitage Trend Test (d)	P=0.064		
Fisher Exact Test (d)		P=0.511	P=0.129

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

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*Skin	(48)	(50)	(50)
Ulcer, acute	4 (8%)		2 (4%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	
Parasitism	7 (15%)	1 (2%)	1 (2%)
Hyperplasia, basal cell		1 (2%)	
Hyperkeratosis	4 (8%)	4 (8%)	2 (4%)
Acanthosis	4 (8%)	4 (8%)	3 (6%)
*Subcutaneous tissue	(48)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, suppurative		1 (2%)	
Inflammation, acute/chronic	3 (6%)		4 (8%)
Inflammation, chronic focal		1 (2%)	
Inflammation, granulomatous focal		1 (2%)	
Fibrosis, multifocal	1 (2%)		1 (2%)
Metaplasia, osseous	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(48)	(50)	(50)
Foreign body, NOS	5 (10%)	1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate	2 (4%)	2 (4%)	2 (4%)
Inflammation, acute focal	2 (4%)		3 (6%)
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal	1 (2%)		
Necrosis, hemorrhagic			1 (2%)
Hyperplasia, epithelial	4 (8%)	4 (8%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(49)	(50)
Inflammation, acute fibrinous			1 (2%)
Hyperplasia, granulocytic	5 (10%)	5 (10%)	6 (12%)
#Spleen	(45)	(47)	(50)
Metaplasia, osseous	1 (2%)		
#Splenic follicles	(45)	(47)	(50)
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Depletion, lymphoid	2 (4%)	1 (2%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)		
#Splenic red pulp	(45)	(47)	(50)
Deposit, NOS			1 (2%)
Depletion, lymphoid		1 (2%)	
Angiectasis		1 (2%)	1 (2%)
Hematopoiesis	15 (33%)	8 (17%)	13 (26%)
#Mandibular lymph node	(41)	(44)	(43)
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Angiectasis			1 (2%)
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Pancreatic lymph node	(41)	(44)	(43)
Hematopoiesis	1 (2%)		
#Mesenteric lymph node	(41)	(44)	(43)
Inflammation, acute necrotizing		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Hematopoiesis	9 (22%)	9 (20%)	13 (30%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Renal lymph node	(41)	(44)	(43)
Plasmacytosis	1 (2%)		
Hematopoiesis	1 (2%)		
#Liver	(48)	(50)	(50)
Hematopoiesis	2 (4%)	3 (6%)	2 (4%)
#Anterior pituitary	(40)	(46)	(49)
Hyperplasia, granulocytic	1 (3%)		
#Thymus	(20)	(33)	(33)
Embryonal duct cyst			1 (3%)
Hemorrhage	1 (5%)		
Depletion, lymphoid	1 (5%)	2 (6%)	3 (9%)
Hyperplasia, epithelial	1 (5%)		
#Thymic lymphocytes	(20)	(33)	(33)
Necrosis, diffuse	1 (5%)		1 (3%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(41)	(44)	(43)
Thrombosis, NOS			1 (2%)
#Auricular appendage	(48)	(50)	(50)
Thrombus, organized		1 (2%)	
#Myocardium	(48)	(50)	(50)
Mineralization	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Degeneration, NOS	2 (4%)	1 (2%)	4 (8%)
*Coronary artery	(48)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Pulmonary artery	(48)	(50)	(50)
Inflammation, chronic diffuse			1 (2%)
*Renal artery	(48)	(50)	(50)
Inflammation, chronic focal			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(46)	(47)	(49)
Inflammation, chronic focal			1 (2%)
#Salivary serous gland	(46)	(47)	(49)
Cytoplasmic vacuolization		1 (2%)	
#Liver	(48)	(50)	(50)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation granulomatous focal	1 (2%)		
Necrosis, focal	2 (4%)		3 (6%)
Basophilic cytoplasmic change	1 (2%)		
Focal cellular change	4 (8%)	1 (2%)	
Angiectasis			1 (2%)
#Liver/hepatocytes	(48)	(50)	(50)
Degeneration, NOS			1 (2%)
Nuclear enlargement			1 (2%)
Cytoplasmic vacuolization	3 (6%)	5 (10%)	
Cell size alteration			1 (2%)
*Gallbladder	(48)	(50)	(50)
Cyst, NOS			2 (4%)
#Bile duct	(48)	(50)	(50)
Hyperplasia, focal			2 (4%)
#Pancreas	(46)	(49)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute diffuse		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(46)	(49)	(48)
Focal cellular change		1 (2%)	
Atrophy, focal	1 (2%)		1 (2%)
Hypertrophy, focal		1 (2%)	
#Periesophageal tissue	(47)	(49)	(49)
Inflammation, acute diffuse			1 (2%)
#Glandular stomach	(45)	(47)	(47)
Mineralization	1 (2%)		
Cyst, NOS	2 (4%)	1 (2%)	
Inflammation, acute focal		1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
#Forestomach	(45)	(47)	(47)
Hyperkeratosis		2 (4%)	
Acanthosis	1 (2%)	2 (4%)	
#Colon	(37)	(45)	(43)
Parasitism	3 (8%)		
URINARY SYSTEM			
#Kidney	(48)	(50)	(50)
Hydronephrosis	4 (8%)		3 (6%)
Inflammation, acute/chronic	2 (4%)		1 (2%)
Nephropathy	2 (4%)	2 (4%)	8 (16%)
Infarct, focal	1 (2%)		
#Kidney/tubule	(48)	(50)	(50)
Mineralization	1 (2%)		
Dilatation, NOS	1 (2%)	2 (4%)	
Necrosis, focal			1 (2%)
Regeneration, NOS	20 (42%)	26 (52%)	25 (50%)
#Kidney/pelvis	(48)	(50)	(50)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
#Urinary bladder	(45)	(47)	(48)
Calculus, microscopic examination			1 (2%)
Inflammation, acute focal	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute/chronic			2 (4%)
Necrosis, diffuse	1 (2%)		
Hyperplasia, epithelial	2 (4%)		1 (2%)
*Prostatic urethra	(48)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Inflammation, acute necrotizing			1 (2%)
Inflammation, acute/chronic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(40)	(46)	(49)
Cyst, NOS	2 (5%)	2 (4%)	1 (2%)
Multiple cysts		1 (2%)	
Focal cellular change		1 (2%)	
#Adrenal/capsule	(48)	(50)	(49)
Degeneration, lipoid	1 (2%)		
Hyperplasia, focal	3 (6%)	2 (4%)	
#Adrenal cortex	(48)	(50)	(49)
Cyst, NOS		1 (2%)	1 (2%)
Degeneration, lipoid	2 (4%)		1 (2%)
Focal cellular change		2 (4%)	
Hypertrophy, focal	3 (6%)	7 (14%)	6 (12%)
Hyperplasia, focal	2 (4%)	4 (8%)	1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(48)	(50)	(49)
Degeneration, lipoid		1 (2%)	1 (2%)
Focal cellular change		1 (2%)	3 (6%)
Hyperplasia, focal	5 (10%)	2 (4%)	10 (20%)
#Thyroid	(46)	(48)	(48)
Follicular cyst, NOS	5 (11%)	4 (8%)	9 (19%)
Hyperplasia, follicular cell	8 (17%)	3 (6%)	11 (23%)
REPRODUCTIVE SYSTEM			
*Penis	(48)	(50)	(50)
Inflammation, acute suppurative			1 (2%)
*Preputial gland	(48)	(50)	(50)
Dilatation/ducts			1 (2%)
Abscess, NOS			2 (4%)
Inflammation, acute/chronic	2 (4%)	1 (2%)	4 (8%)
#Prostate	(48)	(48)	(49)
Hemorrhage	1 (2%)		
Inflammation, acute focal	3 (6%)	3 (6%)	
Inflammation, acute/chronic	3 (6%)		1 (2%)
Inflammation, chronic focal			1 (2%)
*Seminal vesicle	(48)	(50)	(50)
Retention fluid		1 (2%)	1 (2%)
#Testis	(48)	(50)	(50)
Spermatocele			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Degeneration, NOS	9 (19%)	5 (10%)	6 (12%)
*Epididymis	(48)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	3 (6%)		3 (6%)
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous focal	1 (2%)		
Granuloma, spermatic		1 (2%)	
Necrosis, fat			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(49)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Brain	(48)	(49)	(50)
Granuloma, NOS			1 (2%)
Necrosis, focal		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye/crystalline lens	(48)	(50)	(50)
Cataract		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(48)	(50)	(50)
Inflammation, acute focal		1 (2%)	
BODY CAVITIES			
*Mediastinum	(48)	(50)	(50)
Inflammation, acute focal			1 (2%)
Foreign material, NOS		1 (2%)	
*Peritoneum	(48)	(50)	(50)
Inflammation, acute		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES (Continued)			
*Mediastinal pleura	(48)	(50)	(50)
Inflammation, acute necrotizing			1 (2%)
*Pericardium	(48)	(50)	(50)
Inflammation, acute necrotizing			1 (2%)
Foreign material, NOS		1 (2%)	
*Tunica vaginalis	(48)	(50)	(50)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(48)	(50)	(50)
Abscess, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Adipose tissue			
Necrosis, diffuse	1		2
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1		2
Animal missing/no necropsy	2		

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	2 (4%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	3 (6%)
Osteosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type		1 (2%)	2 (4%)
Malignant lymphoma, lymphocytic type	5 (10%)	5 (10%)	
Malignant lymphoma, histiocytic type	3 (6%)		1 (2%)
Malignant lymphoma, mixed type	11 (22%)	15 (30%)	9 (18%)
#Spleen	(49)	(49)	(49)
Malignant lymphoma, mixed type	1 (2%)		
#Jejunum	(47)	(45)	(41)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			1 (2%)
#Spleen	(49)	(49)	(49)
Hemangiosarcoma	1 (2%)		
#Lung	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma	1 (2%)		
Hemangiosarcoma, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)	2 (4%)	4 (8%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)
#Forestomach	(48)	(48)	(43)
Squamous cell papilloma		2 (4%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(47)	(45)	(49)
Adenoma, NOS	1 (2%)		2 (4%)
#Anterior pituitary	(47)	(45)	(49)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	9 (19%)	7 (16%)	6 (12%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal	(50)	(49)	(49)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(50)	(49)	(49)
Adenoma, NOS	3 (6%)	3 (6%)	1 (2%)
#Adrenal medulla	(50)	(49)	(49)
Pheochromocytoma	2 (4%)		1 (2%)
#Thyroid	(49)	(50)	(49)
Follicular cell adenoma		2 (4%)	3 (6%)
Follicular cell carcinoma	1 (2%)		
#Pancreatic islets	(49)	(50)	(46)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
#Uterus	(50)	(49)	(49)
Endometrial stromal polyp	2 (4%)	1 (2%)	3 (6%)
#Ovary	(49)	(48)	(50)
Papillary cystadenoma, NOS		1 (2%)	1 (2%)
Luteoma	1 (2%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(48)
Carcinoma, NOS, invasive			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma	2 (4%)	1 (2%)	
Papillary adenocarcinoma	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Lumbar vertebra	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Fibrosarcoma, metastatic	1 (2%)		
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	8	10
Moribund sacrifice	6	7	9
Terminal sacrifice	36	35	31

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	41	42	32
Total primary tumors	55	56	46
Total animals with benign tumors	22	20	22
Total benign tumors	24	27	29
Total animals with malignant tumors	29	28	16
Total malignant tumors	31	29	17
Total animals with secondary tumors##	2	1	1
Total secondary tumors	2	1	1

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): VEHICLE CONTROL

ANIMAL NUMBER	03 37	03 35	03 39	01 14	02 23	03 33	03 31	01 17	00 09	03 38	00 01	02 29	02 20	00 06	00 02	00 03	00 04	00 05	00 07	00 08	01 10	01 11	01 12	01 13	01 15
WEEKS ON STUDY	06 68	07 71	07 71	07 73	07 76	08 81	08 86	09 91	09 94	09 95	09 96	09 96	10 01	10 02	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma				X												X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Alveolar/bronchiolar carcinoma											X														
Hemangiosarcoma								X																	
Trachea	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	+	+	−	+	+	+	−	+	−	+	−	+	+	+	−	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X				X		
Hepatocellular carcinoma																									
Hemangiosarcoma																									
Hemangiosarcoma, metastatic										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X													X							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																					X				
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	+	+	+	+	−	+	+	+	−	+	+	+	−	+	−	+	+	−	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	N	N	+	+	N	N	N	+	+	N	+	N	+	+	+	N	N	+	N	+
Adenocarcinoma, NOS									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
Papillary adenocarcinoma																								X	
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type							X														X		X		
Malignant lymphoma, histiocytic type	X		X			X																			
Malignant lymphoma, mixed type												X	X	X						X					

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

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

ANIMAL NUMBER	0 1 6	0 1 8	0 1 9	0 2 1	0 2 2	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 3 0	0 3 2	0 3 4	0 3 6	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Fibrosarcoma																									2	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma		X																							2	
Alveolar/bronchiolar carcinoma											X														2	
Hemangiosarcoma																									1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Hemangiosarcoma																									1	
Malignant lymphoma, mixed type																X									1	
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma																									2	
Hepatocellular carcinoma										X															1	
Hemangiosarcoma			X																						1	
Hemangiosarcoma, metastatic																									1	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	47	
Adenoma, NOS			X			X		X							X			X		X			X		10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma, NOS							X							X								X			3	
Pheochromocytoma					X																				2	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Follicular cell carcinoma																				X					1	
Parathyroid	+	+	+	–	+	+	–	–	+	–	–	+	–	+	+	+	+	+	+	–	+	+	+	–	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	N	+	+	+	N	N	+	+	+	N	+	N	N	N	N	N	N	+	+	*50
Adenocarcinoma, NOS																									1	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Endometrial stromal polyp										X											X				2	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Luteoma																									1	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Papillary adenoma																					X		X		2	
Papillary adenocarcinoma																									1	
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Fibrosarcoma, metastatic																									1	
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Malignant lymphoma, lymphocytic type									X		X														5	
Malignant lymphoma, histiocytic type																									3	
Malignant lymphoma, mixed type				X						X		X	X		X						X			X	11	

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): LOW DOSE

ANIMAL NUMBER	0008	0010	0034	0023	0042	0036	0030	0031	0011	0037	0045	0038	0033	0048	0024	0001	0002	0003	0004	0005	0006	0007	0009	0012	0013
WEEKS ON STUDY	0799	0885	0886	0889	0900	0902	0904	0908	0999	0999	0999	1000	1011	1011	1044	1055	1055	1055	1055	1055	1056	1056	1056	1056	1056
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X		X																				X		
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Thymus	+	+	−	+	−	+	−	+	−	+	+	−	+	+	−	+	+	+	+	+	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	N	+	+	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Small intestine	−	+	+	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																						X			
Large intestine	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X																X				X	X	
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma											X							X							
Parathyroid	+	+	−	+	+	+	+	+	+	−	+	−	+	−	−	+	+	−	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	N	+	+	N	N	+	+	N	N	N	+	N	N	+	N	N	N	+	N	+
Adenoma, NOS							X																		
Adenocarcinoma, NOS				X																					
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									X
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS												X													
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
Papillary adenocarcinoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma		X																					X		
Malignant lymphoma, undiffer type					X																				
Malignant lymphoma, lymphocytic type								X		X			X												
Malignant lymphoma, mixed type						X								X	X									X	

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

ANIMAL NUMBER	0144	0155	0166	0177	0188	0199	0200	0211	0222	0255	0266	0277	0288	0299	0322	0355	0399	0400	0411	0433	0444	0466	0477	0499	0500	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X										4
Alveolar/bronchiolar carcinoma							X																			1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X													X		2
Hepatocellular carcinoma													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma												X														2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	45
Adenoma, NOS					X							X					X									7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																		X				X				3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
Parathyroid	+	+	−	−	+	+	−	+	+	+	+	−	+	−	+	−	+	+	+	+	−	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	+	N	+	+	+	N	+	+	N	+	N	N	+	N	+	+	+	N	N	N	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary cystadenoma, NOS																										1
Luteoma		X															X								2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma		X																								1
Papillary adenocarcinoma	X																									1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										2
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type			X							X																5
Malignant lymphoma, mixed type				X	X	X		X			X			X	X	X	X		X		X					15

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED): HIGH DOSE

ANIMAL NUMBER	0011	0013	0014	0015	0110	0002	0006	0299	0500	0118	0331	0333	0335	0288	0466	0499	0211	0115	0332	0074	0088	0099	0111	0122	0133
WEEKS ON STUDY	0666	0688	0711	0788	0799	0822	0844	0877	0877	0902	0966	0996	0996	0997	0997	0997	1011	1033	1033	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma											X														X
Trachea	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	−	−	+	−	+	+	+	−	+	−	−	−	+	+	+	−	−	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma										X															
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	N	N	N	N	N	+	+	+	+	+	N	+	+	N	+	+	N	N	+	+	+
Pancreas	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	−	−	+	−	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	−	+	−	+	−	−	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+
Large intestine	−	−	−	+	+	+	−	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	−	+	−	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X															
Adenoma, NOS								X												X				X	
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	−	−	+	+	−	−	−	+	+	+	+	−	+	+	+	+	−	+	−	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	N	N	N	N	N	+	N	+	N	+	N	N	N	N	N	N	N	N	N	+	N
Uterus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
Luteoma																									
NERVOUS SYSTEM																									
Brain	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undiffer type									X								X								
Malignant lymphoma, histiocytic type																			X						
Malignant lymphoma, mixed type							X											X				X		X	

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

ANIMAL NUMBER	0 1 4	0 1 6	0 1 7	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 3 0	0 3 4	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 7	0 4 8	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50	
Hemangioma													X												1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma		X			X	X																			4	
Alveolar/bronchiolar carcinoma																								X	3	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	46	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	48	
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	35	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma										X	X			X											4	
Hepatocellular carcinoma																									1	
Hemangioma				X																					1	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	43	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, NOS																									1	
Adenoma, NOS									X								X				X	X	X		8	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma, NOS																									1	
Cortical adenoma																			X						1	
Pheochromocytoma																						X			1	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Follicular cell adenoma															X				X						3	
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	–	–	+	–	+	–	+	+	+	+	+	+	+	35	
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	+	N	+	+	N	N	+	+	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp										X			X													3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary cystadenoma, NOS										X																1
Luteoma														X												1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Carcinoma, NOS, invasive																									1	
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50	
Malignant lymphoma, undiffer type																									2	
Malignant lymphoma, histiocytic type																									1	
Malignant lymphoma, mixed type			X							X	X		X						X						9	

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	5.0%	9.4%	11.6%
Terminal Rates (c)	1/36 (3%)	2/36 (6%)	3/31 (10%)
Week of First Observation	91	79	79
Life Table Tests (d)	P=0.236	P=0.359	P=0.293
Incidental Tumor Tests (d)	P=0.336	P=0.500	P=0.392
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.339	P=0.339
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	10.1%	12.0%	20.0%
Terminal Rates (c)	2/36 (6%)	3/36 (8%)	5/31 (16%)
Week of First Observation	91	79	79
Life Table Tests (d)	P=0.169	P=0.521	P=0.215
Incidental Tumor Tests (d)	P=0.259	P=0.621N	P=0.320
Cochran-Armitage Trend Test (d)	P=0.209		
Fisher Exact Test (d)		P=0.500	P=0.262
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	13.1%	12.3%	0.0%
Terminal Rates (c)	4/36 (11%)	2/36 (6%)	0/31 (0%)
Week of First Observation	86	98	
Life Table Tests (d)	P=0.051N	P=0.608N	P=0.046N
Incidental Tumor Tests (d)	P=0.025N	P=0.532N	P=0.031N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.630N	P=0.029N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	6.1%	0.0%	3.0%
Terminal Rates (c)	0/36 (0%)	0/36 (0%)	0/31 (0%)
Week of First Observation	68		103
Life Table Tests (d)	P=0.184N	P=0.118N	P=0.320N
Incidental Tumor Tests (d)	P=0.173N	P=0.362N	P=0.244N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.122N	P=0.309N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	12/50 (24%)	16/50 (32%)	9/50 (18%)
Adjusted Rates (b)	30.7%	41.8%	26.6%
Terminal Rates (c)	9/36 (25%)	14/36 (39%)	7/31 (23%)
Week of First Observation	96	92	84
Life Table Tests (d)	P=0.417N	P=0.260	P=0.438N
Incidental Tumor Tests (d)	P=0.308N	P=0.319	P=0.315N
Cochran-Armitage Trend Test (d)	P=0.281N		
Fisher Exact Test (d)		P=0.252	P=0.312N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	20/50 (40%)	22/50 (44%)	12/50 (24%)
Adjusted Rates (b)	45.9%	52.0%	32.6%
Terminal Rates (c)	13/36 (36%)	16/36 (44%)	7/31 (23%)
Week of First Observation	68	90	84
Life Table Tests (d)	P=0.149N	P=0.449	P=0.153N
Incidental Tumor Tests (d)	P=0.047N	P=0.445	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.059N		
Fisher Exact Test (d)		P=0.420	P=0.067N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	7.4%	4.8%	0.0%
Terminal Rates (c)	1/36 (3%)	1/36 (3%)	0/31 (0%)
Week of First Observation	91	85	
Life Table Tests (d)	P=0.093N	P=0.482N	P=0.137N
Incidental Tumor Tests (d)	P=0.044N	P=0.351N	P=0.072N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.4%	4.8%	6.5%
Terminal Rates (c)	1/36 (3%)	1/36 (3%)	2/31 (6%)
Week of First Observation	91	85	104
Life Table Tests (d)	P=0.448N	P=0.482N	P=0.547N
Incidental Tumor Tests (d)	P=0.341N	P=0.351N	P=0.443N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	5.6%	5.6%	12.9%
Terminal Rates (c)	2/36 (6%)	2/36 (6%)	4/31 (13%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.195	P=0.695	P=0.269
Incidental Tumor Tests (d)	P=0.195	P=0.695	P=0.269
Cochran-Armitage Trend Test (d)	P=0.252		
Fisher Exact Test (d)		P=0.691	P=0.339
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	8.3%	8.3%	15.0%
Terminal Rates (c)	3/36 (8%)	3/36 (8%)	4/31 (13%)
Week of First Observation	104	104	92
Life Table Tests (d)	P=0.218	P=0.664	P=0.285
Incidental Tumor Tests (d)	P=0.241	P=0.664	P=0.329
Cochran-Armitage Trend Test (d)	P=0.283		
Fisher Exact Test (d)		P=0.661	P=0.357
Pituitary Gland: Adenoma			
Overall Rates (a)	9/47 (19%)	7/45 (16%)	6/49 (12%)
Adjusted Rates (b)	25.1%	19.4%	19.4%
Terminal Rates (c)	8/34 (24%)	6/34 (18%)	6/31 (19%)
Week of First Observation	71	86	104
Life Table Tests (d)	P=0.293N	P=0.386N	P=0.350N
Incidental Tumor Tests (d)	P=0.297N	P=0.471N	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.214N		
Fisher Exact Test (d)		P=0.430N	P=0.258N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	9/47 (19%)	7/45 (16%)	7/49 (14%)
Adjusted Rates (b)	25.1%	19.4%	21.3%
Terminal Rates (c)	8/34 (24%)	6/34 (18%)	6/31 (19%)
Week of First Observation	71	86	92
Life Table Tests (d)	P=0.403N	P=0.386N	P=0.464N
Incidental Tumor Tests (d)	P=0.381N	P=0.471N	P=0.452N
Cochran-Armitage Trend Test (d)	P=0.307N		
Fisher Exact Test (d)		P=0.430N	P=0.358N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	8.3%	7.9%	3.2%
Terminal Rates (c)	3/36 (8%)	2/36 (6%)	1/31 (3%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.287N	P=0.656N	P=0.359N
Incidental Tumor Tests (d)	P=0.260N	P=0.650N	P=0.359N
Cochran-Armitage Trend Test (d)	P=0.246N		
Fisher Exact Test (d)		P=0.651	P=0.316N
Adrenal Gland: Adenoma or Cortical Adenoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	2/49 (4%)
Adjusted Rates (b)	8.3%	7.9%	6.5%
Terminal Rates (c)	3/36 (8%)	2/36 (6%)	2/31 (6%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.478N	P=0.656N	P=0.569N
Incidental Tumor Tests (d)	P=0.447N	P=0.650N	P=0.569N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.651	P=0.510N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/49 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	5.1%	9.3%
Terminal Rates (c)	0/36 (0%)	1/36 (3%)	2/31 (6%)
Week of First Observation		99	103
Life Table Tests (d)	P=0.065	P=0.251	P=0.101
Incidental Tumor Tests (d)	P=0.096	P=0.291	P=0.136
Cochran-Armitage Trend Test (d)	P=0.081		
Fisher Exact Test (d)		P=0.253	P=0.121
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	2.8%	5.1%	9.3%
Terminal Rates (c)	1/36 (3%)	1/36 (3%)	2/31 (6%)
Week of First Observation	104	99	103
Life Table Tests (d)	P=0.184	P=0.512	P=0.260
Incidental Tumor Tests (d)	P=0.244	P=0.554	P=0.315
Cochran-Armitage Trend Test (d)	P=0.221		
Fisher Exact Test (d)		P=0.508	P=0.309
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	2/50 (4%)	1/49 (2%)	3/49 (6%)
Adjusted Rates (b)	5.6%	2.8%	9.0%
Terminal Rates (c)	2/36 (6%)	1/36 (3%)	2/31 (6%)
Week of First Observation	104	104	97
Life Table Tests (d)	P=0.349	P=0.500N	P=0.443
Incidental Tumor Tests (d)	P=0.376	P=0.500N	P=0.482
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.508N	P=0.490
Harderian Gland: Papillary Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.3%	5.6%	0.0%
Terminal Rates (c)	3/36 (8%)	2/36 (6%)	0/31 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.100N	P=0.500N	P=0.148N
Incidental Tumor Tests (d)	P=0.100N	P=0.500N	P=0.148N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

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

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Parasitism		2 (4%)	
Hyperplasia, focal	1 (2%)		
Hyperkeratosis	2 (4%)		
Acanthosis	2 (4%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Foreign body, NOS		1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)	2 (4%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, epithelial	3 (6%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Necrosis, focal		1 (2%)	
Hyperplasia, focal			1 (2%)
Myelofibrosis	12 (24%)	19 (39%)	13 (26%)
Hyperplasia, granulocytic	2 (4%)	2 (4%)	2 (4%)
Hyperplasia, reticulum cell		1 (2%)	
#Spleen	(49)	(49)	(49)
Depletion, lymphoid			1 (2%)
#Splenic follicles	(49)	(49)	(49)
Necrosis, focal			1 (2%)
#Splenic red pulp	(49)	(49)	(49)
Hematopoiesis	9 (18%)	6 (12%)	7 (14%)
#Mandibular lymph node	(47)	(48)	(48)
Cyst, NOS	1 (2%)		
#Tracheal lymph node	(47)	(48)	(48)
Edema, NOS		1 (2%)	
#Mediastinal lymph node	(47)	(48)	(48)
Edema, NOS		1 (2%)	
#Pancreatic lymph node	(47)	(48)	(48)
Hematopoiesis		2 (4%)	
#Mesenteric lymph node	(47)	(48)	(48)
Hematopoiesis	2 (4%)	5 (10%)	3 (6%)
#Renal lymph node	(47)	(48)	(48)
Plasmacytosis			1 (2%)
Hematopoiesis			1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis	7 (14%)	7 (14%)	4 (8%)
#Urinary bladder	(48)	(46)	(43)
Hyperplasia, lymphoid	2 (4%)		
#Adrenal	(50)	(49)	(49)
Hematopoiesis			1 (2%)
#Thymus	(41)	(39)	(35)
Depletion, lymphoid	2 (5%)	1 (3%)	3 (9%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Mineralization	1 (2%)		
#Heart/atrium	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
#Myocardium	(50)	(50)	(50)
Inflammation, multifocal	1 (2%)		
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic			1 (2%)
Degeneration, NOS	1 (2%)	5 (10%)	
*Pulmonary artery	(50)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
*Uterine artery	(50)	(50)	(50)
Perivasculitis	1 (2%)		
*Mesentery	(50)	(50)	(50)
Perivasculitis	1 (2%)		
#Uterus/endometrium	(50)	(49)	(49)
Thrombosis, NOS	1 (2%)		
#Thyroid	(49)	(50)	(49)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(48)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
#Liver	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal		2 (4%)	2 (4%)
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous focal			1 (2%)
Necrosis, focal	2 (4%)	2 (4%)	1 (2%)
Focal cellular change			2 (4%)
#Liver/hepatocytes	(50)	(50)	(50)
Cytoplasmic vacuolization	5 (10%)	2 (4%)	2 (4%)
Hyperplasia, focal			1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
#Bile duct	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
#Pancreas	(49)	(50)	(46)
Cystic ducts		1 (2%)	
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal			2 (4%)
#Pancreatic acinus	(49)	(50)	(46)
Cytoplasmic vacuolization			1 (2%)
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Atrophy, focal	1 (2%)	3 (6%)	3 (7%)
Atrophy, diffuse	1 (2%)		
Hypertrophy, focal	1 (2%)		
#Esophagus/muscularis	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
#Gastric fundal gland	(48)	(48)	(43)
Cyst, NOS		1 (2%)	
#Glandular stomach	(48)	(48)	(43)
Necrosis, focal		1 (2%)	
Dysplasia, NOS		1 (2%)	
#Forestomach	(48)	(48)	(43)
Hyperplasia, epithelial	2 (4%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)		
Glomerulonephritis, acute			1 (2%)
Nephropathy	1 (2%)		2 (4%)
Infarct, focal	1 (2%)	2 (4%)	
#Kidney/capsule	(50)	(50)	(49)
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic focal			1 (2%)
#Kidney/cortex	(50)	(50)	(49)
Inflammation, chronic focal		1 (2%)	
Metaplasia, osseous		1 (2%)	
#Kidney/tubule	(50)	(50)	(49)
Degeneration, NOS		1 (2%)	1 (2%)
Regeneration, NOS	13 (26%)	9 (18%)	15 (31%)
#Urinary bladder	(48)	(46)	(43)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder/submucosa	(48)	(46)	(43)
Edema, NOS			1 (2%)
#Urinary bladder/serosa	(48)	(46)	(43)
Inflammation, granulomatous focal		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(47)	(45)	(49)
Cyst, NOS	1 (2%)		
#Anterior pituitary	(47)	(45)	(49)
Cyst, NOS	2 (4%)		1 (2%)
Multiple cysts		1 (2%)	
Hemorrhagic cyst			1 (2%)
Degeneration, NOS			1 (2%)
Hyperplasia, NOS	7 (15%)	7 (16%)	5 (10%)
Hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
#Adrenal	(50)	(49)	(49)
Hyperplasia, cystic		1 (2%)	
#Adrenal/capsule	(50)	(49)	(49)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, focal		1 (2%)	
#Adrenal cortex	(50)	(49)	(49)
Accessory structure			1 (2%)
Cyst, NOS	1 (2%)	1 (2%)	1 (2%)
Degeneration, lipoid	1 (2%)	2 (4%)	
Hypertrophy, focal	5 (10%)	8 (16%)	6 (12%)
Hyperplasia, focal	2 (4%)	1 (2%)	2 (4%)
#Adrenal medulla	(50)	(49)	(49)
Hyperplasia, focal	3 (6%)	2 (4%)	2 (4%)
#Periadrenal tissue	(50)	(49)	(49)
Inflammation, acute/chronic			1 (2%)
#Thyroid	(49)	(50)	(49)
Embryonal duct cyst	2 (4%)		1 (2%)
Follicular cyst, NOS	5 (10%)	11 (22%)	9 (18%)
Inflammation, chronic focal		2 (4%)	
Hyperplasia, C-cell		1 (2%)	
Hyperplasia, follicular cell	12 (24%)	7 (14%)	3 (6%)
#Parathyroid	(36)	(37)	(35)
Embryonal duct cyst		1 (3%)	
#Pancreatic islets	(49)	(50)	(46)
Hyperplasia, focal			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic		1 (2%)	
#Uterus	(50)	(49)	(49)
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Angiectasis		1 (2%)	4 (8%)
#Cervix uteri	(50)	(49)	(49)
Inflammation, acute focal	1 (2%)		
#Endometrial gland	(50)	(49)	(49)
Hyperplasia, cystic	45 (90%)	46 (94%)	43 (88%)
#Fallopian tube	(50)	(49)	(49)
Inflammation, chronic diffuse	1 (2%)		
#Ovary	(49)	(48)	(50)
Follicular cyst, NOS	17 (35%)	14 (29%)	16 (32%)
Parovarian cyst	7 (14%)	5 (10%)	5 (10%)
Abscess, NOS	1 (2%)		7 (14%)
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Inflammation, chronic diffuse	1 (2%)		
Angiectasis		1 (2%)	2 (4%)
#Ovary/follicle	(49)	(48)	(50)
Hemorrhagic cyst	7 (14%)	4 (8%)	4 (8%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(50)	(50)	(48)
Atrophy, pressure	1 (2%)	1 (2%)	2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
*Eye, posterior chamber	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Hyperostosis		1 (2%)	1 (2%)
*Sternum	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Femur	(50)	(50)	(50)
Hyperostosis		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF XYLENES (MIXED) (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute/chronic			2 (4%)
*Peritoneum	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)	1 (2%)	6 (12%)
*Mesentery	(50)	(50)	(50)
Cyst, NOS			1 (2%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX E

GENETIC TOXICOLOGY OF XYLENES (MIXED)

TABLE E1. MUTAGENICITY OF XYLENES (MIXED) IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	82 ± 2.4	166 ± 9.2	155 ± 3.5
	3	84 ± 6.7	159 ± 2.5	163 ± 11.1
	10	90 ± 9.1	175 ± 7.3	155 ± 6.1
	33	88 ± 4.7	155 ± 14.1	149 ± 10.8
	100	79 ± 4.7	122 ± 3.4	(c) 118 ± 11.9
	200	(c) 84 ± 5.8	(c) 124 ± 11.9	(c) 98 ± 0.3
TA1535	0	16 ± 3.4	15 ± 0.0	14 ± 4.4
	3	18 ± 3.8	14 ± 3.2	15 ± 1.7
	10	21 ± 0.0	10 ± 0.7	14 ± 1.8
	33	18 ± 2.1	13 ± 1.9	14 ± 2.8
	100	14 ± 3.2	(c) 10 ± 3.1	(c) 12 ± 3.2
	200	(c) 11 ± 2.0	(c) 11 ± 1.2	(c) 5 ± 1.5
TA97	0	95 ± 3.3	177 ± 8.1	144 ± 9.8
	3	111 ± 4.4	194 ± 7.2	145 ± 5.4
	10	104 ± 5.9	152 ± 9.5	162 ± 5.8
	33	(c) 98 ± 7.2	146 ± 20.3	134 ± 14.8
	100	(c) 106 ± 4.9	(c) 120 ± 10.4	(c) 132 ± 5.2
	200	(c) 93 ± 10.1	(c) 108 ± 5.8	(c) 112 ± 5.2
TA98	0	18 ± 2.3	28 ± 5.2	39 ± 3.4
	3	20 ± 2.7	23 ± 2.1	37 ± 3.3
	10	20 ± 3.8	29 ± 4.9	33 ± 2.9
	33	25 ± 3.5	28 ± 1.0	35 ± 2.2
	100	(c) 18 ± 1.8	28 ± 1.7	35 ± 3.2
	200	(c) 18 ± 3.7	26 ± 2.0	(c) 27 ± 5.9

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

TABLE E2. MUTAGENICITY OF *o*-XYLENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	131 ± 4.1	129 ± 6.4	131 ± 5.2
	1.0	126 ± 9.8	--	--
	3.3	136 ± 10.5	134 ± 5.2	142 ± 2.6
	10.0	128 ± 5.9	135 ± 6.4	133 ± 10.4
	33.0	139 ± 11.9	141 ± 3.5	129 ± 7.4
	100.0	141 ± 14.8	124 ± 7.2	130 ± 9.9
	333.0	--	(c) 106 ± 6.6	(c) 119 ± 9.3
TA1535	0.0	24 ± 2.0	8 ± 1.7	11 ± 1.2
	1.0	26 ± 1.7	--	--
	3.3	25 ± 2.7	11 ± 3.2	10 ± 1.3
	10.0	22 ± 2.9	9 ± 0.6	11 ± 1.5
	33.0	20 ± 2.8	12 ± 1.5	10 ± 2.2
	100.0	26 ± 2.9	10 ± 1.2	9 ± 2.3
	333.0	--	(c) 10 ± 1.5	(c) 7 ± 2.0
TA1537	0.0	6 ± 1.2	7 ± 1.0	8 ± 1.7
	1.0	8 ± 1.5	--	--
	3.3	10 ± 0.3	7 ± 0.7	9 ± 1.3
	10.0	9 ± 1.2	7 ± 1.5	8 ± 1.0
	33.0	5 ± 1.0	5 ± 1.2	7 ± 1.5
	100.0	7 ± 1.8	5 ± 0.9	7 ± 0.3
	333.0	--	(c) 10 ± 1.9	(c) 7 ± 1.9
TA98	0.0	16 ± 3.0	25 ± 2.9	25 ± 2.7
	1.0	16 ± 5.0	--	--
	3.3	17 ± 2.1	23 ± 1.2	23 ± 3.8
	10.0	20 ± 3.3	29 ± 1.2	24 ± 0.3
	33.0	21 ± 1.5	22 ± 2.5	23 ± 2.0
	100.0	17 ± 2.0	28 ± 3.3	24 ± 1.5
	333.0	--	(c) 19 ± 0.7	25 ± 2.4

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

TABLE E3. MUTAGENICITY OF *m*-XYLENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	144 ± 16.2	136 ± 4.8	130 ± 3.2
	0.3	125 ± 4.7	119 ± 8.6	121 ± 6.5
	1.0	120 ± 12.0	122 ± 12.3	108 ± 13.2
	3.0	141 ± 10.5	144 ± 7.6	128 ± 12.0
	10.0	127 ± 13.3	126 ± 2.9	114 ± 9.1
	33.0	126 ± 9.2	118 ± 8.4	106 ± 8.4
TA1535	0.0	21 ± 4.4	15 ± 1.7	6 ± 0.9
	0.3	22 ± 3.1	10 ± 3.5	8 ± 0.9
	1.0	17 ± 3.5	10 ± 1.5	11 ± 0.0
	3.0	22 ± 2.2	14 ± 1.5	12 ± 1.2
	10.0	21 ± 1.3	10 ± 2.1	11 ± 0.9
	33.0	18 ± 2.4	13 ± 1.7	11 ± 3.2
TA1537	0.0	6 ± 1.0	11 ± 3.8	7 ± 0.9
	0.3	7 ± 1.8	7 ± 1.2	6 ± 0.6
	1.0	7 ± 0.7	8 ± 2.3	7 ± 0.6
	3.0	6 ± 0.9	9 ± 1.0	6 ± 0.7
	10.0	5 ± 1.2	11 ± 3.5	8 ± 1.5
	33.0	8 ± 0.6	7 ± 1.2	7 ± 1.5
TA98	0.0	18 ± 3.8	25 ± 3.5	21 ± 3.8
	0.3	22 ± 3.8	27 ± 0.3	22 ± 2.4
	1.0	14 ± 2.0	22 ± 2.3	21 ± 0.6
	3.0	19 ± 0.3	26 ± 3.4	27 ± 5.6
	10.0	17 ± 2.1	21 ± 1.2	23 ± 3.8
	33.0	15 ± 1.3	24 ± 2.0	30 ± 0.3

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

TABLE E4. MUTAGENICITY OF *p*-XYLENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0.0	97 ± 2.8	110 ± 15.6	85 ± 5.7
	1.0	122 ± 4.0	--	--
	3.3	101 ± 7.9	112 ± 11.5	80 ± 2.2
	10.0	104 ± 10.6	116 ± 7.5	86 ± 3.2
	33.0	102 ± 9.5	110 ± 5.7	86 ± 3.5
	100.0	(c) 88 ± 5.2	102 ± 3.5	77 ± 8.4
	200.0	--	(c) 67 ± 2.6	(c) 73 ± 6.4
TA1535	0.0	18 ± 2.8	10 ± 2.2	9 ± 1.2
	1.0	18 ± 1.5	--	--
	3.3	21 ± 2.5	9 ± 0.7	9 ± 2.0
	10.0	22 ± 3.0	12 ± 1.7	10 ± 2.1
	33.0	25 ± 4.3	7 ± 1.5	12 ± 1.8
	100.0	17 ± 5.7	11 ± 2.8	12 ± 2.1
	200.0	--	(c) 7 ± 1.2	(c) 9 ± 2.6
TA1537	0.0	5 ± 0.9	9 ± 1.9	8 ± 2.9
	1.0	6 ± 0.6	--	--
	3.3	7 ± 0.9	4 ± 0.9	9 ± 2.1
	10.0	6 ± 2.0	7 ± 2.3	6 ± 1.3
	33.0	7 ± 0.6	8 ± 2.0	10 ± 1.2
	100.0	7 ± 2.0	6 ± 0.7	8 ± 1.5
	200.0	--	(c) 3 ± 0.9	9 ± 0.7
TA98	0.0	15 ± 1.5	27 ± 3.4	25 ± 3.5
	1.0	19 ± 2.1	--	--
	3.3	22 ± 3.5	26 ± 2.9	29 ± 2.1
	10.0	14 ± 1.9	26 ± 3.1	27 ± 1.5
	33.0	21 ± 4.8	22 ± 4.9	27 ± 3.3
	100.0	(c) 16 ± 1.0	28 ± 4.7	19 ± 0.0
	200.0	--	(c) 21 ± 4.5	(c) 22 ± 1.8

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

TABLE E5. MUTAGENICITY OF ETHYLBENZENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	147 ± 4.0	111 ± 2.1	114 ± 8.2
	10	161 ± 5.8	100 ± 5.0	120 ± 11.5
	33	147 ± 4.1	110 ± 8.1	137 ± 22.7
	100	157 ± 3.2	105 ± 2.3	109 ± 7.1
	333	118 ± 11.5	111 ± 4.7	97 ± 7.1
	666	(c) 74 ± 4.0	--	--
	1,000	--	77 ± 8.2	98 ± 1.7
TA1535	0	29 ± 3.8	9 ± 2.0	7 ± 1.5
	10	26 ± 3.2	8 ± 0.7	9 ± 1.3
	33	19 ± 2.5	9 ± 3.0	6 ± 0.7
	100	25 ± 2.5	5 ± 0.6	8 ± 1.5
	333	14 ± 0.3	8 ± 2.4	9 ± 1.2
	666	(c) 0 ± 0.0	--	--
	1,000	--	5 ± 1.5	5 ± 1.8
TA97	0	111 ± 9.5	200 ± 10.0	195 ± 12.3
	10	120 ± 16.3	190 ± 15.1	194 ± 10.3
	33	144 ± 2.4	193 ± 5.3	195 ± 3.5
	100	124 ± 5.2	179 ± 7.8	191 ± 7.1
	333	108 ± 9.1	211 ± 3.3	173 ± 3.5
	666	(c) 6 ± 5.7	--	--
	1,000	--	189 ± 23.4	124 ± 9.6
TA98	0	29 ± 5.5	34 ± 3.3	24 ± 3.2
	10	27 ± 4.4	26 ± 1.8	29 ± 1.8
	33	35 ± 7.8	34 ± 3.5	26 ± 0.6
	100	16 ± 2.1	32 ± 2.3	28 ± 4.7
	333	20 ± 8.4	30 ± 2.3	23 ± 3.0
	666	(c) 27 ± 14.5	--	--
	1,000	--	26 ± 1.5	21 ± 2.3

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

TABLE E6. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY ETHYLBENZENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell (d)	Dose (µg/ml)	SCE/Cell (d)
DMSO		DMSO	
1%	11.1	1%	10.6
Ethylbenzene		Ethylbenzene	
75.5	11.0	125.0	11.2
99.5	10.4	137.0	10.6
125.0	11.8	150.0	10.3
Mitomycin C		Cyclophosphamide	
0.001	15.5	0.350	14.5
0.010	44.0	2.000	31.8

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

TABLE E7. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY ETHYLBENZENE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
Medium	1 (1)	Medium	2 (2)
DMSO		DMSO	
1%	3 (3)	1%	3 (3)
Ethylbenzene		Ethylbenzene	
75	1 (1)	75	4 (4)
100	3 (3)	100	1 (1)
125	5 (5)	125	1 (1)
Mitomycin C		Cyclophosphamide	
1.000	32 (22)	50	46 (36)

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

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

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

II. Results

Results are presented in Table F1.

TABLE F1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF XYLENES (MIXED) (a)

	Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS			
	6	--	None positive
	12	--	None positive
	18	--	None positive
	24	4/10	KRV
MICE			
	6	--	None positive
	12	3/9 2/9	Reo 3 GDVII
	18	--	None positive
	24	4/10	MHV

(a) Blood samples were taken from sentinel animals (five/sex) at 6, 12, and 18 months after the start of dosing and from the vehicle control animals (five/sex) just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX G

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

Pelleted Diet: June 1980 to July 1982

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

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
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

TABLE 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 activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.04 ± 0.75	22.7-25.1	24
Crude fat (percent by weight)	4.84 ± 0.80	4.1-5.7	24
Crude fiber (percent by weight)	3.40 ± 0.29	2.9-4.3	24
Ash (percent by weight)	6.56 ± 0.50	5.7-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,146 ± 2,291	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.6 ± 3.3	7.4-27.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.29 ± 0.21	0.81-1.69	24
Phosphorus (percent)	1.00 ± 0.07	0.86-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.7	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (July 22, 1981) was not analyzed for thiamine.

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

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.42 ± 0.21	<0.05-1.06	24
Cadmium (ppm)	0.09 ± 0.02	<0.05-0.10	24
Lead (ppm)	0.99 ± 0.72	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.31 ± 0.08	0.14-0.52	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	8.15 ± 3.65	2.1-17.0	24
Nitrite nitrogen (ppm) (c)	2.23 ± 1.59	0.4-6.9	24
BHA (ppm) (d,e)	4.55 ± 3.59	<0.4-13.0	24
BHT (ppm) (e)	2.55 ± 1.40	0.8-5.9	24
Aerobic plate count (CFU/g)	40,592 ± 32,056	4,900-120,000	24
Coliform (MPN/g) (f)	30.3 ± 53.2	<3-240	23
Coliform (MPN/g) (g)	74.8 ± 224.5	<3-1,100	24
E. coli (MPN/g) (h)	<3		24
Total nitrosamines (ppb) (i, j)	7.20 ± 7.04	<0.8-24.5	21
Total nitrosamines (ppb) (i,k)	29.40 ± 64.76	<0.8-273.3	24
N-Nitrosodimethylamine (ppb) (i, j)	5.67 ± 6.49	0.8-20.0	21
N-Nitrosodimethylamine (ppb) (i,k)	27.67 ± 64.38	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.35 ± 0.92	0-3.5	24
Pesticides (ppm)			
α-BHC (a,l)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (m)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCB's (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (m)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (n)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

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

(a) All values were less than the detection limit, which is given in the table as the mean.
(b) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Two batches contained less than 0.5 ppm.
(e) Source of contamination: soy oil and fish meal
(f) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80 (MPN = most probable number).
(g) Mean, standard deviation, and range include the high value listed in footnote (f).
(h) All values were less than 3 MPN/g.
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb obtained for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(k) Mean, standard deviation, and range include the very high values given in footnote j.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(n) Eleven batches contained more than 0.05 ppm.

APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The archival data and pathology materials from the 2-year gavage studies of xylenes (mixed) in rats and mice were audited for completeness, consistency, and accuracy. Battelle Columbus Laboratories performed the studies under an NCI subcontract with Tracor Jitco, Inc. The studies, conducted from June 1980 to July 1982, began before NTP required compliance with the Good Laboratory Practice regulations in October 1981. The audit was conducted from September 30 through October 8, 1985, at the NTP Archives, Research Triangle Park, North Carolina, and involved the following personnel from Program Resources, Inc.: W. Oller, Ph.D.; K. Connor; J. Winegar, B.S.; S. Corson, H.T. (ASCP); K. Pace, B.S.; and C. Rafferty, A.S.; and J. Sagartz, D.V.M. (Veritas Laboratories). The full audit report was reviewed and approved by the National Toxicology Program and is on file in Research Triangle Park, North Carolina.

For the inlife toxicology review, 10% of the body weight data and 10% of the clinical observation records were audited. All records regarding mortality, tumor observations, environmental conditions, sentinel animal data, animal receipt, quarantine, randomization, and identification were audited.

For the chemistry audit, all available chemistry data were reviewed, including Midwest Research Institute microfiche, chemical receipt, chemical usage, bulk chemical reanalysis, chemical/vehicle analyses, and surplus chemical transmittal data. Ten percent of dose calculations were verified. Bulk chemical reanalysis substantiated that chemical identity and composition were consistent throughout the studies.

All wet tissue bags were inventoried. Ten percent of wet tissues were examined for animal identification, potential untrimmed lesions, and discrepancies between gross observations and microscopic diagnoses. All slides were matched with blocks for high dose and vehicle control groups of both species. All Individual Animal Data Records were reviewed. The pathology audit revealed eight unresolved discrepancies between gross observations and microscopic diagnoses in rats. In addition, untrimmed, potentially neoplastic lesions were seen in three low dose male rats and one vehicle control male mouse. Because these lesions were all at different tissue sites, none of which had even a marginal indication of a chemical-related effect, they were not pursued further.

In conclusion, the audit revealed no major problems with the conduct of the studies or with the collection and documentation of the experimental data. No discrepancies were found that influenced interpretation of the results of these studies.

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