NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 375

TOXICOLOGY AND CARCINOGENESIS STUDIES OF VINYL TOLUENE (MIXED ISOMERS)

(65%-71% *META*-ISOMER AND 32%-35% *PARA*-ISOMER)

(CAS NO. 25013-15-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

NTP TECHNICAL REPORT

ON THE

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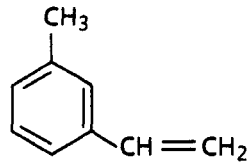
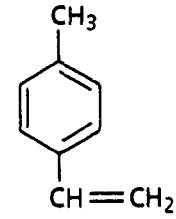


meta-Vinyl Toluene
(65%-71%)



para-Vinyl Toluene
(32%-35%)

VINYL TOLUENE (mixed isomers)

C_9H_{10} Molecular weight 118.2

Synonyms: 3-Vinyl toluene and 4-vinyl toluene (mixed isomers)

ABSTRACT

Vinyl toluene is used as a monomer in the plastics and surface-coating industries. Toxicology and carcinogenesis studies were conducted by exposing groups of F344/N rats and B6C3F$_1$ mice of each sex to vinyl toluene (mixed isomers: 65%-71% *meta* and 32%-35% *para*) by inhalation 6 hours per day, 5 days per week, for 15 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse L5178Y cells, and Chinese hamster ovary (CHO) cells.

Fifteen-Day Studies: Rats were exposed to 0, 200, 400, 800, or 1,300 ppm vinyl toluene, and mice were exposed to 0, 10, 25, 50, 100, or 200 ppm. All rats lived to the end of the studies. The mean body weights at necropsy of rats exposed to 400-1,300 ppm were 13%-19% lower than that of controls for males and 9%-13% lower for females. Most male rats exposed to 1,300 ppm had centrilobular necrosis and focal inflammatory cell infiltration of the liver, whereas minimal centrilobular vacuolization of the liver was seen in all female rats exposed to 1,300 ppm. Dysplasia of the bronchial epithelial lining, chronic bronchitis, and lymphoid hyperplasia of the lung were observed in all rats exposed to 1,300 ppm.

Three of five male mice exposed to 200 ppm vinyl toluene died before the end of the studies. Four of five male mice exposed to 200 ppm had moderate-to-severe hepatocellular necrosis; all female mice exposed to 200 ppm had hyperplasia of the epithelium of the intrapulmonary bronchi and centrilobular necrosis, vacuolization, and inflammatory cell infiltrates in the liver.

Thirteen-Week Studies: Rats were exposed to 0, 25, 60, 160, 400, or 1,000 ppm vinyl toluene. All rats lived to the end of the studies. The final mean body weights of rats exposed to 400-1,000 ppm were 8%-19% lower than that of controls for males and 6%-12% lower for females. Relative liver weights for rats at 1,000 ppm were significantly greater than those for controls. The severity of nephropathy was increased in male rats exposed to 160, 400, or 1,000 ppm. Compound-related lesions were not observed in female rats.

Mice were exposed to 0, 10, 25, 60, or 160 ppm vinyl toluene. The final mean body weights of mice exposed to 25-160 ppm were 12%-20% lower than that of controls for males and 13%-16% lower for females. Inflammation of the lung was observed in 5/10 male and 3/9 female mice exposed to 160 ppm. Metaplasia of the nasal turbinates was seen in all exposed groups.

Based on these results, 2-year studies were conducted by exposing groups of 49 or 50 rats of each sex to 0, 100, or 300 ppm vinyl toluene by inhalation, 6 hours per day, 5 days per week for 103 weeks. Groups of 50 mice of each sex were exposed to 0, 10, or 25 ppm on the same schedule.

Body Weights and Survival in the Two-Year Studies: Mean body weights of male rats exposed to 300 ppm vinyl toluene and those of female rats exposed to 100 and 300 ppm were generally 4%-11% lower than those of controls. No significant differences in survival were seen between any groups of rats of either sex (male: control, 19/49; low dose, 17/50; high dose, 19/50; female: 31/50; 28/50; 26/50). Mean body weights of mice exposed to 25 ppm were 10%-23% lower than those of controls after week 8, whereas mice exposed to 10 ppm showed a weight decrement that was generally less than 10%. The survival of male mice exposed to 25 ppm was significantly greater than that of controls. No other significant differences in survival were seen between any groups of mice of either sex (male: 33/50; 30/50; 41/50; female: 36/50; 37/50; 34/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Degenerative and nonneoplastic proliferative lesions of the nasal mucosa were observed at increased incidences in exposed rats. These lesions included diffuse hyperplasia (goblet cell) of the respiratory epithelium with intraepithelial mucous cysts and focal erosion of the olfactory epithelium with cystic dilatation (cysts) of the Bowman's glands. Focal respiratory epithelial metaplasia of the olfactory epithelium was seen in some exposed males, and cells with homogeneous eosinophilic cytoplasm in the olfactory epithelium occurred at increased incidences in exposed female rats. Neoplasms of the nasal mucosa were not seen in male or female rats.

There were no chemically related increases in neoplasm incidence in exposed male or female rats.

Degenerative and inflammatory lesions of the nasal mucoca were observed at increased incidences in exposed mice. These lesions included focal chronic active inflammation and diffuse hyperplasia of the respiratory epithelium. Chronic active inflammation of the bronchioles occurred in many exposed mice but not in controls. Neoplasms of the nasal passage were not observed in mice.

There were no chemically related increases in neoplasm incidence in exposed male or female mice. Exposure-related decreased incidences included alveolar/bronchiolar neoplasms (control, 12/50; 10 ppm, 5/49; 25 ppm, 2/49) and malignant lymphomas (7/50; 3/50; 0/50) in males and hepatocellular neoplasms (9/48; 5/16; 2/49) in females.

Genetic Toxicology: Vinyl toluene did not induce gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without exogenous metabolic activation (S9). Vinyl toluene was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y/TK cells in the absence of S9; it was not tested with S9. Vinyl toluene did not induce sister chromatid exchanges or chromosomal aberrations in CHO cells with or without S9.

Conclusions: Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** for male or female F344/N rats exposed to 100 or 300 ppm vinyl toluene and *no evidence of carcinogenic activity* for male or female B6C3F$_1$ mice exposed to 10 or 25 ppm.

There was evidence of chemical-related toxicity to the nasal passage in both rats and mice.

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

SUMMARY OF THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Exposure concentrations			
0, 100, or 300 ppm vinyl toluene, 6 h/d, 5 d/wk	0, 100, or 300 ppm vinyl toluene, 6 h/d, 5 d/wk	0, 10, or 25 ppm vinyl toluene, 6 h/d, 5 d/wk	0, 10, or 25 ppm vinyl toluene, 6 h/d, 5 d/wk
Body weights in the 2-year study			
Exposed groups lower than controls	Exposed groups lower than controls	Exposed groups lower than controls	Exposed groups lower than controls
Survival in the 2-year study			
19/49; 17/50; 19/50	31/50; 28/50; 26/50	33/50; 30/50; 41/50	36/50; 37/50; 34/50
Nonneoplastic effects			
Hyperplasia of respiratory epithelium; erosion and cysts of olfactory epithelium; metaplasia of olfactory epithelium	Hyperplasia of respiratory epithelium; erosion and cysts of olfactory epithelium	Hyperplasia of respiratory epithelium; chronic active inflammation of nasal passage and bronchioles	Hyperplasia of respiratory epithelium; chronic active inflammation of nasal passage and bronchioles
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence
Other considerations			
		Exposure-related decreased incidences of lymphomas and pulmonary neoplasms	Exposure-related decreased incidences of liver neoplasms

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Vinyl Toluene is based on 13-week studies that began in January 1981 and ended in April 1981 and on 2-year studies that began in December 1981 and ended in November 1983 at Midwest Research Institute (Kansas City, MO).

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The members of the Peer Review Panel who evaluated the draft Technical Report on Vinyl Toluene on November 20, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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

On November 20, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of vinyl toluene received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. G. Boorman, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats or mice).

Dr. Ashby, a principal reviewer, agreed with the conclusions. He commented on the the decreased incidences of three tumor types in exposed groups of mice--lymphomas and pulmonary neoplasms in males and liver neoplasms in females. He said that the evidence for classifying vinyl toluene as a mutagen was quite slim.

Dr. Garman, the second principal reviewer, agreed with the conclusions. He asked for an explanation of why liquid vinyl toluene entered the inhalation chambers. He said that this raised questions about the technical conduct of the studies. Dr. Boorman explained that there was a dosing accident with one chamber at week 21 of the studies whereby six mice were exposed to the liquid chemical; these animals were removed from the studies. Dr. Boorman did not believe that this isolated incident reflected negatively on the overall conduct of the studies.

Dr. Ashby moved that the Technical Report on vinyl toluene be accepted with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Garman seconded the motion, which was accepted unanimously.

I. INTRODUCTION

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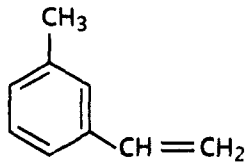
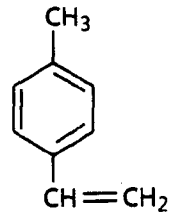


meta-Vinyl Toluene
(65%-71%)



para-Vinyl Toluene
(32%-35%)

VINYL TOLUENE (mixed isomers)

C_9H_{10} Molecular weight 118.2

Synonyms: 3-Vinyl toluene and 4-vinyl toluene (mixed isomers)

Use, Production, and Properties

Vinyl toluene (methylstyrene) is used as a monomer in the plastics and surface-coating industries (Kuney, 1983) and as a component in insecticides (Clayton and Clayton, 1981). As many as 73,000 employees in 7,000 plants are potentially exposed to vinyl toluene (NIOSH, 1989).

Vinyl toluene is produced by the dehydrogenation of *m*- and *p*-ethyltoluene and by catalytic reforming. In 1976, it was estimated that approximately 50% of vinyl toluene was used as a chemical intermediate for unsaturated polyester resins, 40% for alkyd coating resins, and 10% as a chemical intermediate for drying oils (TDB, 1982). U.S. production of vinyl toluene alkyd resins in 1982 was nearly 31 billion pounds, dry weight (USITC, 1983).

Vinyl toluene is a colorless, combustible liquid with a strong, disagreeable odor. It is an alkylated benzene that occurs as a mixture primarily of the *m*- (50%-70%) and *p*- (30%-45%) isomers, with a density of 0.8946 at 25° C, a boiling point of 167°-172° C, and a vapor pressure of 1.15 mm mercury at 20° C. At elevated temperatures, vapors mixed with air may be explosive, and polymerization may occur under explosive expansion.

Metabolism

After rats received a single intraperitoneal injection of 50 mg/kg, 55% of the dose was found as urinary metabolites, mainly in the first 6 hours; at higher doses, slightly smaller percentages were found (Heinonen, 1984). The principal urinary metabolites were thioethers (25%), *p*-methylmandelic acid (5.7%), *p*-methylphenylglyoxylic acid (11.9%), *p*-methylbenzoyl glycine (9.3%), *p*-methylphenylacetyl glycine (2.5%), and *p*-vinylbenzoyl glycine (1%). The excretion of these metabolites was prevented by pretreatment with an inhibitor of the cytochrome P450 monoxygenases. Further, vinyl toluene was found to bind to hepatic cytochrome P450, and the reduced glutathione content of the liver and kidney was decreased in rats after a single intraperitoneal injection (Heinonen and Vainio, 1980). These findings suggest that metabolism of vinyl toluene is catalyzed by cytochrome P450, producing vinyl toluene-7,8-oxide as the main reactive intermediate, with subsequent conjugation to glutathione or hydration to diols (Heinonen, 1984). Proposed metabolic pathways for vinyl toluene in rats are presented in Figures 1 and 2.

Systemic Toxicity

In humans, vinyl toluene is irritating to the eyes, upper respiratory tract, and skin at concentrations greater than 400 ppm, with prolonged or high doses causing depression of the central nervous system (Clayton and Clayton, 1981; Mackison et al., 1981). The American Conference of Governmental Industrial Hygienists recommends a threshold limit value (time-weighted average) of 50 ppm (240 mg/m^3) for

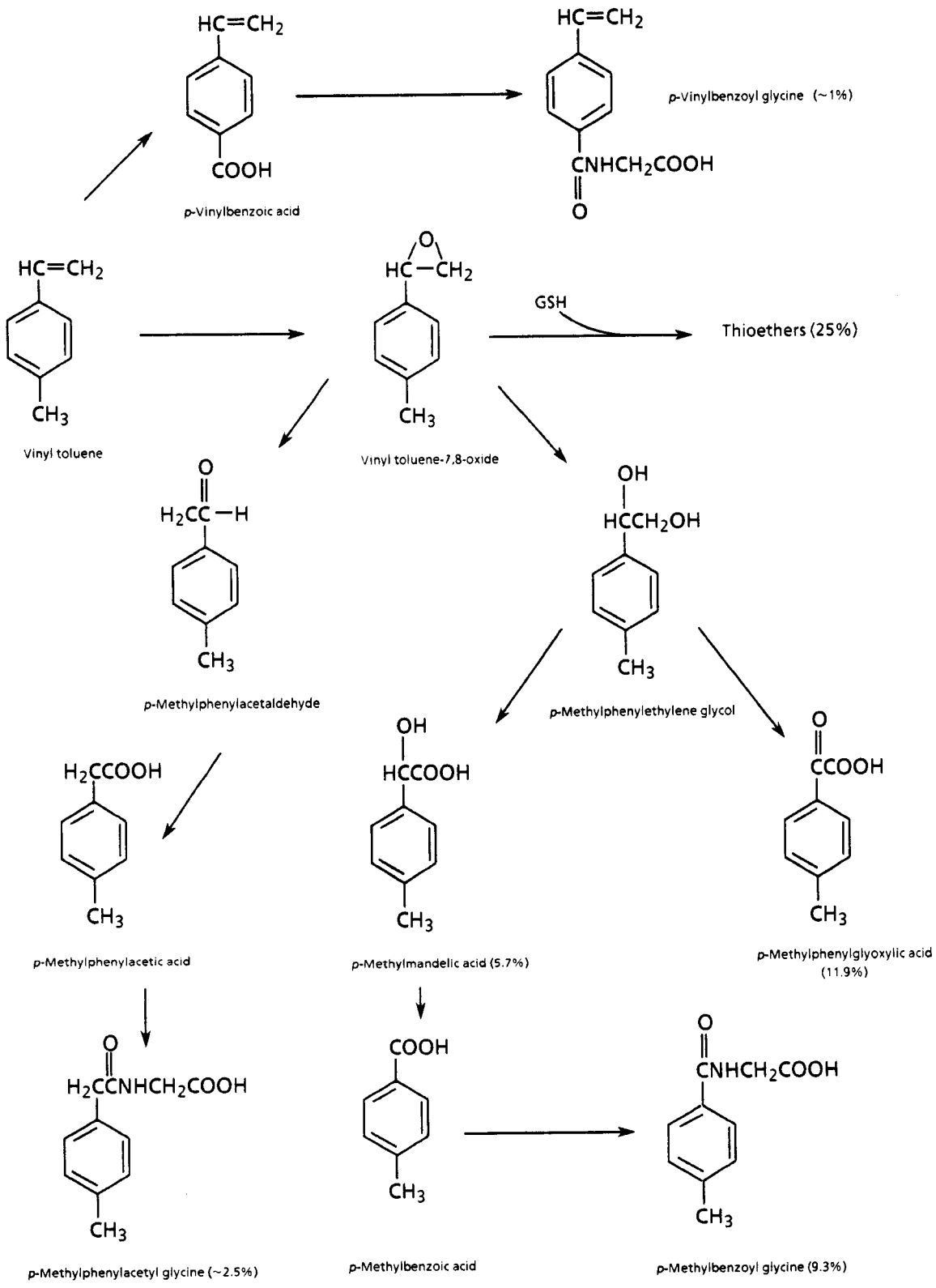


FIGURE 1. MAIN METABOLIC PATHWAYS OF VINYL TOLUENE IN RATS
(adapted from Heinonen, 1984)

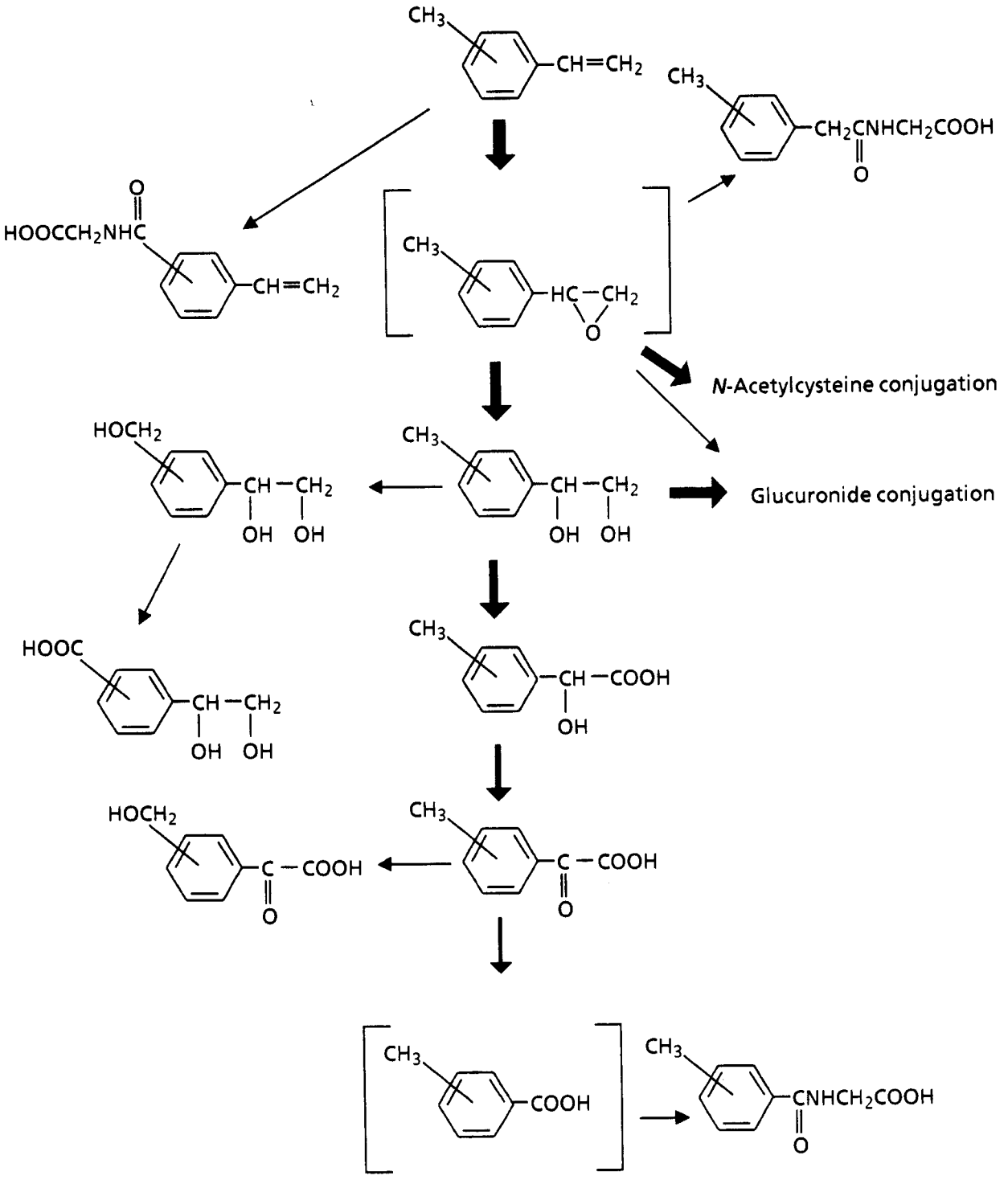


FIGURE 2. METABOLISM OF VINYL TOLUENE IN RATS

(Adapted from Bergemalm-Rynell and Steen, 1982)

occupational exposure to vinyl toluene (ACGIH, 1980). The recommended short-term exposure limit is 100 ppm (485 mg/m^3). The current Occupational Safety and Health Administration standard is 100 ppm, averaged over an 8-hour work shift (Mackison et al., 1981).

The oral LD_{50} in rats is approximately 4 g/kg (Wolf et al., 1956). Inhalation exposure (approximately 100 exposures of up to 8 hours) at 1,250 ppm leads to fatty degeneration of the liver in guinea pigs, rabbits, monkeys, and rats and to death in rats.

Genetic Toxicology

Vinyl toluene (mixture of the *o*-, *m*-, and *p*-isomers) was negative in bacterial mutagenicity assays conducted with or without S9 activation (Norppa et al., 1981; Knaap et al., 1985; Zeiger et al., 1987) and in the Drosophila sex-linked recessive lethal assay (Norppa et al., 1981; Knaap et al., 1985). In contrast, the results obtained from the limited number of mammalian cell mutagenicity assays conducted with vinyl toluene were generally positive. This may reflect greater control for volatility in these assays, thus assuring adequate exposure to the chemical, or differences in chemical activation capabilities. Induction of gene mutation in L5178Y mouse lymphoma cells was reported, although this effect was observed only at high concentrations that produced severe toxicity (McGregor et al., 1988). Induction of sister chromatid exchanges (SCEs) and chromosomal aberrations in human lymphocytes was reported (Norppa, 1981a; Norppa and Vainio, 1983), but negative results were obtained for these two endpoints in Chinese hamster ovary (CHO) cells (Appendix H, Tables H3 and H4). Intraperitoneal injection of vinyl toluene in male C57BL/6 mice produced a significant increase in micronucleated polychromatic erythrocytes in the bone marrow (Norppa, 1981b).

Mutagenicity information is available on two of the metabolites of vinyl toluene: *p*- and *m*-(epoxyethyl) toluene. The *p*-isomer was positive for induction of gene mutations in bacteria (Sugiura et al., 1978; Sugiura and Goto, 1981; Tamura et al., 1982) and hamster V79 cells (Sugiura et al., 1979) and was reported to induce SCEs in human lymphocytes (Norppa and Vainio, 1983). The *m*-isomer was also reported to be a bacterial mutagen (Sugiura and Goto, 1981). All these tests were done in the absence of S9 activation. The fact that metabolites of vinyl toluene are mutagenic in bacteria although the parent compound is not implies a requirement for metabolism that apparently was available in the mammalian systems tested but was not supplied, or was ineffective, in the S9 fraction added to bacterial cultures.

This pattern of activity (mutagenic activity of metabolites but not the parent compound in bacterial systems) reflects the pattern seen with the structural analog styrene, which is not mutagenic in bacterial systems unless measures are taken to stabilize the mutagenic metabolite styrene oxide after its formation by the S9 mix (Dunkel et al., 1985). Many reports confirm the mutagenicity of styrene oxide in Salmonella (Vainio et al., 1976; Stoltz and Withey, 1977; de Meester et al., 1977; Loprieno et al., 1978), whereas the data for styrene glycol (produced by further metabolism of the styrene oxide) are uniformly negative (Milvy and Garro, 1976; Vainio et al., 1976; De Flora et al., 1984). Styrene also has been reported to induce SCEs and chromosomal aberrations in mammalian cells in vitro (Linnainmaa et al., 1978; Matsuoka et al., 1979; Norppa et al., 1980; Norppa and Vainio, 1983; Pohlova et al., 1985) and in vivo (Meretoja et al., 1978; Conner et al., 1980; Sharief et al., 1986); results from National Toxicology Program cytogenetic tests with CHO cells in vitro were, as with vinyl toluene, negative for induction of SCEs and chromosomal aberrations (NTP unpublished data). Norppa (1981b) reported induction of micronuclei in the bone marrow of C57BL/6 mice injected with styrene. The presumed mutagenic metabolite, styrene oxide, was also positive for these cytogenetic endpoints in vitro and in vivo (Loprieno et al., 1978; Linnainmaa et al., 1978; Norppa et al., 1980, 1983; Norppa, 1981a; Pohlova et al., 1985).

Long-Term Toxicity and Carcinogenicity

The long-term toxicity, carcinogenicity, and neoplasm-promoting potential of vinyl toluene

have previously not been adequately tested in animals.

Study Rationale

Vinyl toluene was selected for evaluation of long-term toxicity and carcinogenicity by the National Cancer Institute because of its widespread production, its increasing use as a replacement for styrene, the potential for human exposure, and the lack of epidemiologic data or animal studies. The inhalation route of exposure was chosen to mimic the potential route of exposure in humans.

II. MATERIALS AND METHODS

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PROCUREMENT AND CHARACTERIZATION OF VINYL TOLUENE

The vinyl toluene (mixed isomers) used in these studies, referred to in this Technical Report as vinyl toluene, was manufactured by Dow Chemical Company (Midland, MI). One of the three lots used was obtained from Missouri Solvents and Chemical Company, and two lots were obtained from Chem Central. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). The first lot was used for the short-term studies, the second lot was used for the first 20 months of the 2-year studies, and the third lot was used for the remainder of the 2-year studies.

The identity of all lots as a mixture of *m*-vinyl toluene and *p*-vinyl toluene was confirmed by infrared, ultraviolet, and nuclear magnetic resonance spectroscopic analysis. The purity of all lots was determined to be approximately 99% (combined 65%-71% *meta*- and 32%-35% *para*-isomers) by elemental analyses, Karl Fischer water analysis, the American Society for Testing and Materials (ASTM) visual test for polymers in styrene (limit of detection, 0.001% polymer), and gas chromatography. The content of the inhibitor, *t*-butylcatechol, was determined by a semiquantitative colorimetric method to range from 30 to 70 ppm.

Stability studies performed by gas chromatography indicated that vinyl toluene was stable as a bulk chemical when stored protected from light for 2 weeks at temperatures up to 25° C. Results of periodic analysis by infrared spectroscopy, gas chromatography, determination of inhibitor concentration, and polymer concentration indicated no significant degradation of the study material throughout the studies.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Vapor Generation System

Vinyl toluene vapor was generated by using either a J-tube or a gas dispersion-type system in which heated air was passed through liquid vinyl toluene. The vapor then entered the airstream near the top of the chamber and was mixed in the chamber plenum before entering the exposure area of the chamber. In the 2-year studies, secondary flasks were used to further dilute and mix the vapor with filtered air before it was channeled to the appropriate intake port of the study chambers (Hazleton 2000®, Lab Products, Inc.) (Table G2). An individual generation system contained within an enclosure specifically designed for operation under negative pressure was used for each chamber.

Vapor Concentration Monitoring

The concentration of vinyl toluene in the chambers and the exposure room was monitored by an automatic sampling system coupled to a gas chromatograph (Varian 2700) equipped with a flame ionization detector and a 3% SP2250 column (100% Carbowax 20M-TPA column for the short-term studies). The gas chromatographic system was standardized daily by manually injecting solutions of vinyl toluene in *n*-hexane. Samples from the study chamber atmospheres were pulled from the chambers by a vacuum pump. During the 2-year studies, each study chamber atmosphere, a sample of the control chamber atmosphere, and a sample of workroom air were analyzed every 30 minutes during the 6-hour exposure. The distribution of the mean daily concentrations in the chambers is summarized in Table G3.

Chamber Atmosphere Characterization

Uniformity of vapor concentration in each exposure chamber and at each position with animals present was measured periodically throughout the studies by the same system used for daily concentration monitoring to validate the use of single-port sampling for daily concentration monitoring. The coefficients of variation were always found to be less than 10%.

Tests were conducted for potential oxidation products and their possible hydration products, including vinyl toluene glycol, *m*-methylphenethyl alcohol, *p*-methylphenethyl alcohol, and α,*p*-dimethylbenzyl alcohol. An analytic sample

was collected by passing a 400-ppm vinyl toluene atmosphere through an impinger in a dry ice/acetone bath at 12 liters/minute for 30 minutes; the sample was extracted with chloroform and analyzed by gas chromatography using a flame ionization detector and a 3% SP2250 column. None of the potential degradation products was determined to be present at concentrations greater than 0.05% of the vinyl toluene concentration.

Polymers present in a 1,000-ppm chamber atmosphere were determined after an impinger sample was condensed and the ASTM test (ASTM, 1970) and gel-permeation chromatography were performed on the condensate. The condensate was negative in the ASTM test (less than 0.1% polymer), and no high molecular weight substances were found by gel-permeation chromatography (Waters GPC columns, 254-nm ultraviolet detector, and tetrahydrofuran mobile phase).

The aerosol concentration was determined by drawing a 300-ppm vinyl toluene atmosphere through a seven-stage, multijet cascade impactor. Gas chromatographic analysis performed on the contents of the collection slip of each stage and of the final filter indicated that no aerosol was present on any given stage at greater than 0.037% (w/v) of total vinyl toluene sampled (total less than 0.26% for the seven stages).

Residual concentrations of vinyl toluene were determined in the chambers after the 6-hour exposure period. The concentration dropped rapidly; the residual chemical concentration in the chambers was generally less than the detectable level (0.01 ppm) 3 hours after the generators had been stopped and the chambers purged for 1 hour.

FIFTEEN-DAY STUDIES

Groups of five rats of each sex were exposed to air containing vinyl toluene at target concentrations of 0, 200, 400, 800, or 1,300 ppm, 6 hours per day for 10 days over a 15-day period. Groups of five mice of each sex were exposed to air containing vinyl toluene at target concentrations of 0, 10, 25, 50, 100, or 200 ppm on the same schedule. Rats and mice were observed once per day and were weighed before exposure, after 1 week, and at the end of the studies. A necropsy was performed on all animals. Histopathologic examinations were performed on rats in the 1,300-ppm groups, mice in the 200-ppm groups, and one male mouse and one female mouse in the control groups. Further details are presented in Table 1.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated inhalation of vinyl toluene and to determine the concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained at 4-5 weeks of age, observed for 20 days, and assigned to groups according to tables of random numbers. Feed was available ad libitum during nonexposure periods; water was available at all times.

Groups of 10 rats of each sex were exposed to air containing vinyl toluene at target concentrations of 0, 25, 60, 160, 400, or 1,000 ppm, 6 hours per day, 5 days per week for 13 weeks (64 exposures). Groups of 10 mice of each sex were exposed to air containing vinyl toluene at target concentrations of 0, 10, 25, 60, or 160 ppm on the same schedule. Further experimental details are summarized in Table 1.

Animals were observed one or two times per day; moribund animals were killed. Clinical signs were recorded once per week. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Histologic examinations were performed on all rats in the control and 1,000-ppm groups, 9 male mice and 10 female mice in the control groups, and all mice in the 25-, 60-, and 160-ppm groups. Tissues and groups examined are listed in Table 1.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF VINYL TOLUENE

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	49 or 50 males and 50 females of each species
Exposure Concentrations		
Rats--0, 200, 400, 800, or 1,300 ppm vinyl toluene (mixed isomers) by inhalation; mice--0, 10, 25, 50, 100, or 200 ppm	Rats--0, 25, 60, 160, 400, or 1,000 ppm vinyl toluene (mixed isomers) by inhalation; mice--0, 10, 25, 60, or 160 ppm	Rats--0, 100, or 300 ppm vinyl toluene (mixed isomers) by inhalation; mice--0, 10, or 25 ppm
Date of First Exposure		
Rats--9/30/80; mice--8/20/80	1/6/81	12/1/81
Date of Last Exposure		
Rats--10/14/80; mice--9/3/80	4/7/81	Rats--11/21/83; mice--11/23/83
Duration of Exposure		
6 h/d for 10 d over 15 d	6 h/d for 64 d over 13 wk	6 h/d, 5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 1 × d; weighed initially and 1 × wk thereafter	Observed 1 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and 1 × mo thereafter
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams performed on all animals in the high dose groups and on 1 male and 1 female in mouse control groups. Tissues examined include: brain, duodenum, heart, kidneys, lungs, pancreas, and stomach for rats and mice. Brain and liver weighed at necropsy	Necropsy performed on all animals; histologic exams performed on all control and high dose animals and on mice in the 25- and 60-ppm groups. Tissues examined include: adrenal glands, bone, brain, cecum, colon, duodenum, epididymis/seminal vesicles/prostate/testes or oviduct/ovaries/uterus, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, mesentery, nasal passage, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, rectum, salivary glands, skin, spinal cord, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder	Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups and animals dying before mo 20 or 21: adrenal glands, bone, brain, cecum, colon, duodenum, epididymis/seminal vesicles/prostate/testes or oviduct/ovaries/uterus, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, mesentery, nasal passage, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, rectum, salivary glands, skin, spinal cord, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Lungs and nasal passage examined for low dose rats and mice
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
Animal Source		
Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Frederick Cancer Research Facility (Frederick, MD)
Study Laboratory		
Midwest Research Institute	Midwest Research Institute	Midwest Research Institute

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF VINYL TOLUENE (Continued)

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Method of Animal Identification		
Ear tag	Ear tag	Ear tag
Time Held Before Study		
Rats--21 d; mice--28 d	20 d	19 d
Age When Placed on Study		
Rats--7-8 wk; mice--9-10 wk	Rats--7-8 wk; mice--8-9 wk	Rats--9-10 wk; mice--8-9 wk
Age When Killed		
Rats--9-10 wk; mice--11-12 wk	Rats--20-21 wk; mice--21-22 wk	Rats--113-114 wk; mice--112-113 wk
Necropsy Dates		
Rats--10/15/80; mice--9/4/80-9/5/80	4/8/81-4/10/81	Rats--11/28/83-12/1/83; mice--12/1/83-12/5/83
Method of Animal Distribution		
Assigned to groups according to a table of random numbers	Assigned to groups according to tables of random numbers and then placed in cages in numerical order	Same as 13-wk studies
Diet		
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum except during exposure periods	Same as 15-d studies	Same as 15-d studies and Purina Rodent Laboratory Chow® (Ralston Purina Co., St. Louis, MO)
Water		
Water bottles; available ad libitum during nonexposure periods	Automatic watering system (Edstrom Industries, Waterford, WI) or water bottles; available ad libitum	Same as 13-wk studies
Chambers		
Stainless steel Hazleton 2000® (Hazleton Systems, Aberdeen, MD)	Young and Bertke (Cincinnati, OH); Stainless steel Hazleton 2000® (Hazleton Systems, Aberdeen, MD)	Same as 15-d studies
Animals per Cage		
1	1 (or 5 for 10-ppm mice)	1
Other Chemicals on Study in the Same Room		
None	None	None
Chamber Environment		
Rats: temp--72°-78° F; hum--30%-48%; fluorescent light 12 h/d; 10-17 room air changes/h during exposure periods; mice: temp--68°-76° F; hum--35%-53%; fluorescent light 12 h/d; 10-18 room air changes/h during exposure periods	Temp--69°-81° F; hum--30%-51%; fluorescent light 12 h/d; 10-18 room air changes/h during exposure periods	Temp--65°-80° F; hum--29%-94%; fluorescent light 12 h/d; >10 room air changes/h

II. MATERIALS AND METHODS

TWO-YEAR STUDIES

Study Design

Groups of 49 or 50 male and 50 female rats were exposed to air containing vinyl toluene at concentrations of 0 (chamber controls), 100, or 300 ppm, 6 hours per day, 5 days per week for 103 weeks. Groups of 50 mice of each sex were exposed to air containing vinyl toluene at concentrations of 0 (chamber controls), 10, or 25 ppm on the same schedule. Actual concentrations are summarized in Table G3.

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 Frederick Cancer Research Facility. 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 6-7 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. 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 9-10 weeks of age and mice at 8-9 weeks of age.

Animal Maintenance

Rats and mice were housed individually. Feed (Appendix F) and water were available ad libitum. Serologic analyses were performed as described in Appendix E. Cages were rotated one position clockwise once per day, except on weekends and holidays, from December 1, 1981, until February 18, 1982, and once per week thereafter. Further details of animal maintenance are summarized in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Individual body weights were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead. One male from the control group was found to have been missexed and was discarded.

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. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) were performed on all high dose and control animals and on low dose animals dying through month 20 (male rats and female mice) or 21 (female rats and male mice) of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. The nasal passage and lung were considered potential target organs for chemically related neoplastic and nonneoplastic effects and were examined histopathologically in the low concentration groups.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues (nasal passage and lung), and all tissues from a randomly selected 10% of the animals from each control and high concentration group were reevaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs and in the randomly selected 10% of animals.

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

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. 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: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were

used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

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

III. RESULTS

RATS

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

FIFTEEN-DAY STUDIES

All rats lived to the end of the studies (Table 2). Lethargy, excessive lacrimation, and red-staining (porphyrin) material around the nose and mouth were observed for rats exposed to 1,300 ppm. The mean body weights at necropsy of rats exposed to 400-1,300 ppm were 13%-19% lower than that of the controls for males and 10%-13% lower for females.

Absolute and relative liver weights were significantly increased for rats exposed to 1,300 ppm (Table I1). Four of five male rats exposed to 1,300 ppm had centrilobular necrosis and focal inflammatory cell infiltration of the liver. Minimal-to-slight centrilobular vacuolization of the liver was seen in 5/5 female rats exposed to 1,300 ppm. Dysplasia of the bronchial epithelium, chronic bronchitis, and lymphoid hyperplasia of the lung were observed in all rats exposed to 1,300 ppm. The severity was minimal to slight in males and minimal in females. Because of decreased weight gain at 1,300 ppm (19% for males, 13% for females), the top concentration selected for the 13-week studies was 1,000 ppm.

THIRTEEN-WEEK STUDIES

All rats lived to the end of the studies (Table 3). The final mean body weights of rats exposed to 160, 400, or 1,000 ppm were 6%, 8%, or 19% lower than that of controls for males and 5%, 6%, or 12% lower for females. Excessive lacrimation, palpebral closure, and rough hair coats were seen in rats exposed to 1,000 ppm. Relative liver weights, but not absolute weights, for rats exposed to 1,000 ppm were significantly greater than those for controls (Table I2). A mild nephropathy characterized by increased tubular casts was found in male rats exposed to 160, 400, or 1,000 ppm. No compound-related lesions were observed in female rats.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIFTEEN-DAY INHALATION STUDIES OF VINYL TOLUENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams)			Necropsy Weight Relative to Controls (percent)
		Initial (b)	Necropsy	Change (c)	
MALE					
0	5/5	148	211	+63	
200	5/5	145	203	+58	96
400	5/5	142	183	+41	87
800	5/5	145	183	+38	87
1,300	5/5	146	171	+25	81
FEMALE					
0	5/5	114	144	+30	
200	5/5	110	132	+22	92
400	5/5	111	129	+18	90
800	5/5	114	131	+17	91
1,300	5/5	113	125	+12	87

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

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

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Necropsy	Change (c)	Necropsy Weight Relative to Controls (percent)
MALE					
0	10/10	159 ± 3	375 ± 11	+216 ± 9	
25	10/10	155 ± 2	375 ± 7	+220 ± 6	100
60	10/10	159 ± 3	372 ± 6	+213 ± 5	99
160	10/10	158 ± 2	353 ± 6	+195 ± 5	94
400	10/10	155 ± 2	346 ± 9	+191 ± 7	92
1,000	10/10	155 ± 4	302 ± 10	+147 ± 7	81
FEMALE					
0	10/10	125 ± 2	214 ± 5	+89 ± 3	
25	10/10	124 ± 2	212 ± 4	+88 ± 3	99
60	10/10	125 ± 2	209 ± 3	+84 ± 2	98
160	10/10	124 ± 1	204 ± 1	+80 ± 1	95
400	10/10	123 ± 1	201 ± 2	+78 ± 2	94
1,000	10/10	122 ± 1	189 ± 4	+67 ± 3	88

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

Dose Selection Rationale: Because of lower mean body weight gain at 160 ppm or more, increased relative liver weights at 1,000 ppm, and mild nephrotoxicity in males, inhalation exposure concentrations selected for rats for the 2-year studies were 100 and 300 ppm vinyl toluene, 6 hours per day, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of male rats exposed to 300 ppm were generally 4%-8% lower than those of controls after week 2 (Table 4 and Figure 3). Mean body weights of female rats exposed to 100 and 300 ppm were generally 5%-11% lower than those of controls after week 21. No compound-related clinical signs were observed.

TABLE 4. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

Weeks on Study	Chamber Control		100 ppm			300 ppm		
	Av. Wt. (grams)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls	Number of Survivors
MALE								
0	185	50	191	103	50	185	100	50
1	210	50	210	100	50	205	98	50
2	232	50	229	99	50	218	94	50
3	250	50	247	99	50	234	94	50
4	266	50	263	99	50	251	94	50
5	279	50	276	99	50	262	94	50
6	289	50	288	100	50	273	94	50
7	298	50	298	100	50	284	95	50
8	307	50	310	101	50	294	96	50
9	321	49	316	98	50	300	93	50
10	331	49	324	98	50	309	93	50
11	337	49	335	99	50	318	94	50
12	347	49	342	99	50	326	94	50
13	352	49	346	98	50	333	95	50
17	374	49	352	94	50	369	99	50
21	390	49	388	99	50	367	94	50
25	403	49	401	100	50	381	95	50
29	409	49	408	100	50	387	95	50
33	416	49	418	100	50	397	95	50
37	421	49	427	101	50	406	96	50
41	434	49	432	100	50	410	94	50
45	440	49	436	99	50	415	94	50
49	441	49	434	98	50	418	95	50
53	446	48	442	99	50	422	95	50
57	441	48	447	101	49	430	98	50
61	457	47	451	99	49	435	95	50
65	462	47	456	99	49	438	95	50
69	460	47	468	102	46	442	96	50
73	459	45	459	100	45	440	96	49
77	467	40	452	97	41	441	94	46
81	463	38	458	99	39	442	95	41
85	457	38	457	100	37	441	96	39
89	449	34	444	99	34	431	96	37
93	463	28	439	95	30	424	92	33
97	434	25	379	87	27	433	100	26
101	443	21	417	94	18	414	93	22
Mean for weeks								
1-13	294		291	99.0		277	94.2	
17-49	414		411	99.3		394	95.2	
53-101	454		444	97.8		433	95.4	
FEMALE								
0	132	50	133	101	50	134	102	50
1	144	50	142	99	50	142	99	50
2	153	50	148	97	50	146	95	50
3	161	50	155	96	50	153	95	50
4	167	50	162	97	50	160	96	50
5	173	50	166	96	50	165	95	50
6	176	50	170	97	50	169	96	50
7	182	50	175	96	50	173	95	50
8	186	50	181	97	50	178	96	50
9	190	50	184	97	50	182	96	50
10	195	50	187	96	50	185	95	50
11	197	50	191	97	50	187	95	50
12	201	50	191	95	50	190	95	50
13	204	50	195	96	50	193	95	50
17	207	50	201	97	50	204	99	50
21	222	50	210	95	50	208	94	50
25	230	49	217	94	50	214	93	50
29	232	49	220	95	50	219	94	50
33	239	49	225	94	50	224	94	50
37	247	49	234	95	50	230	93	50
41	254	49	240	94	50	238	94	50
45	272	49	242	89	50	246	90	50
49	270	49	249	92	50	249	92	50
53	285	49	258	91	50	262	92	50
57	295	49	267	91	50	271	92	50
61	305	49	276	90	49	275	90	49
65	312	48	282	90	49	280	90	47
69	321	47	290	90	49	283	88	47
73	323	47	294	91	47	291	90	44
77	326	47	297	91	46	293	90	43
81	330	45	301	91	44	297	90	43
85	334	43	305	91	43	299	90	40
89	333	42	302	91	43	298	89	38
93	332	39	306	92	39	304	92	35
97	316	38	305	97	36	300	95	35
101	329	34	298	91	30	303	92	30
Mean for weeks								
1-13	179		173	96.6		171	95.5	
17-49	241		226	93.8		226	93.8	
53-101	319		291	91.2		290	90.9	

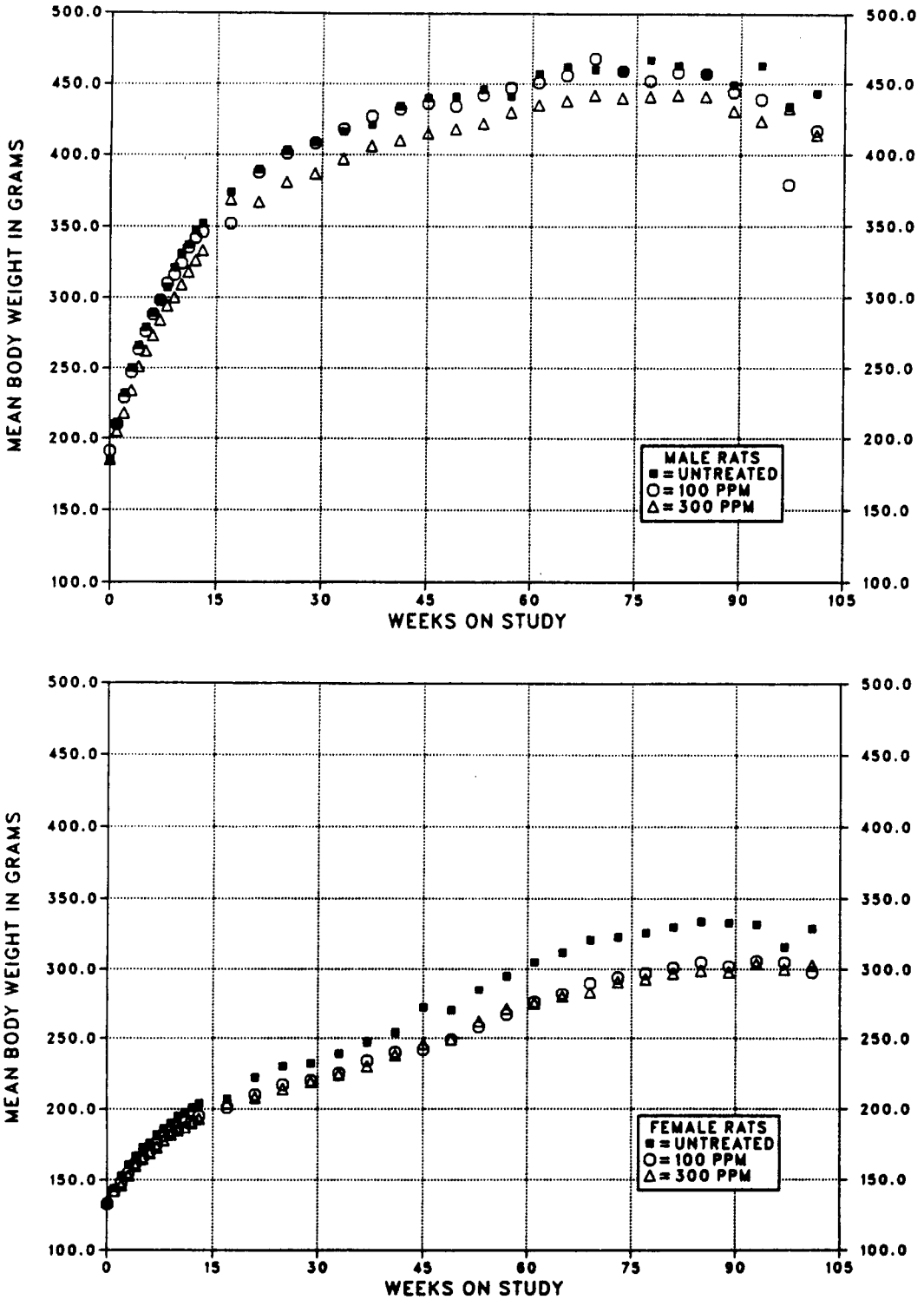

FIGURE 3. GROWTH CURVES FOR RATS EXPOSED TO VINYL TOLUENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats exposed to vinyl toluene at the concentrations used in these studies and for controls are shown in Table 5 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were seen between any groups of rats of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nasal passage, kidney, and urinary bladder.

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

TABLE 5. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

	Chamber Control	100 ppm	300 ppm
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	6	4	3
Moribund kills	24	29	28
Animals missexed	1	0	0
Animals surviving to study termination	19	17	19
Mean survival (days)	648	648	665
Survival P values (b)	0.762	0.825	0.878
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	3	1	6
Moribund kills	16	21	18
Animals surviving to study termination	31	28	26
Mean survival (days)	677	683	667
Survival P values (b)	0.372	0.733	0.399

(a) First day of termination period: 728
(b) The result of the life table trend test is in the chamber control column, and the results of the life table pairwise comparisons with the chamber controls are in the dosed columns.

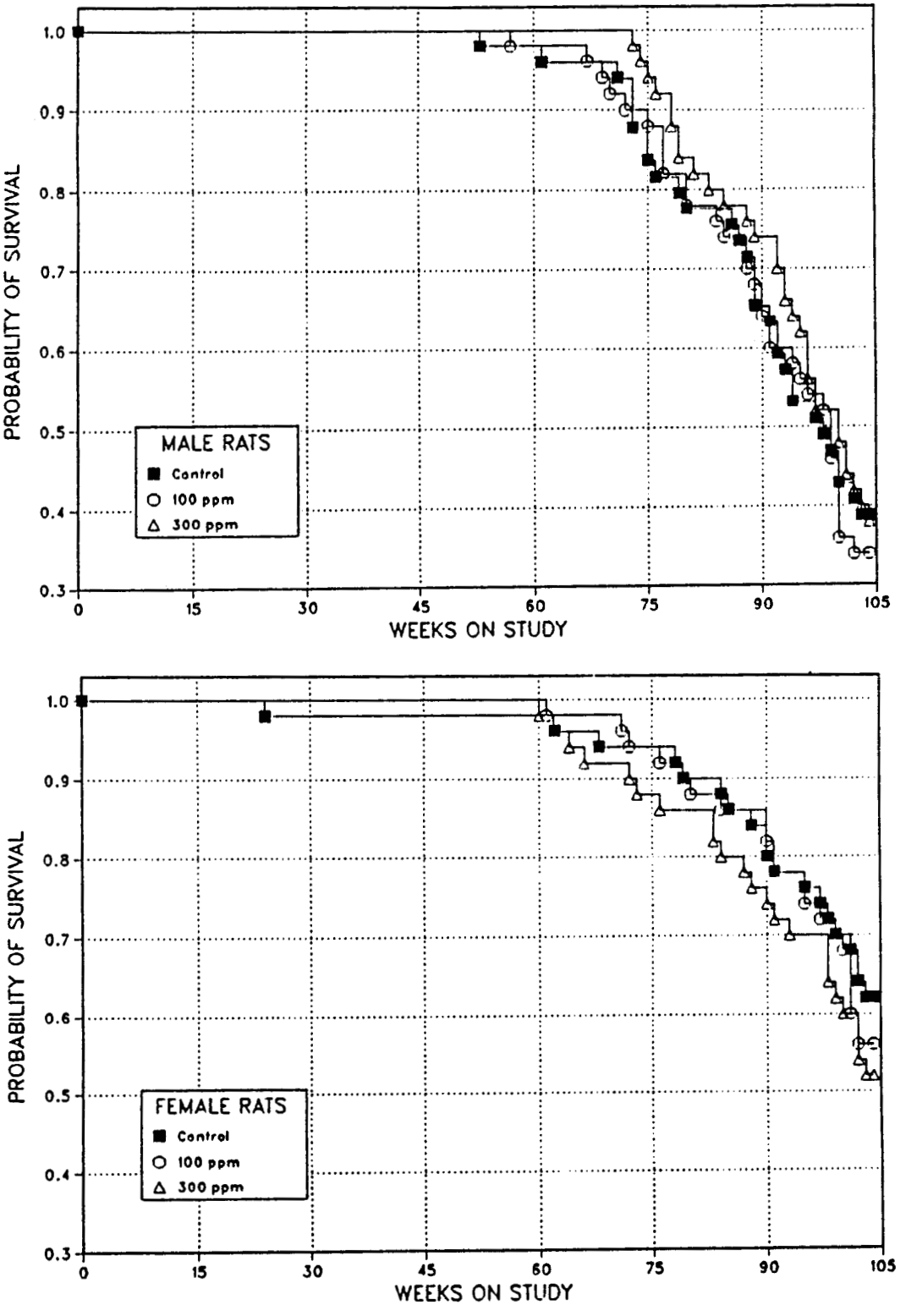

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO VINYL TOLUENE BY INHALATION FOR TWO YEARS

Nasal Passage: Degenerative and nonneoplastic proliferative lesions occurred at increased incidences in the nasal mucosa of exposed rats (Table 6). Hyperplasia of the respiratory epithelium was usually diffuse and was characterized by increased numbers of goblet cells and increased height of the epithelium; in some males, slight folding of the epithelium (papillary hyperplasia) was seen. The cysts were small, intraepithelial glandlike structures distended with mucus. Lesions involving the olfactory epithelium occurred primarily in the anterior region along the dorsal meatus. The olfactory epithelium was focally eroded; the underlying Bowman's glands were cystically dilated, and the glandular epithelium was replaced by ciliated columnar cells (olfactory epithelium, cyst). In some exposed male rats, the olfactory epithelium was focally replaced by pseudostratified ciliated columnar epithelium (respiratory epithelial metaplasia). In the olfactory epithelium of exposed female rats, there were increased numbers of cells with homogeneous eosinophilic cytoplasm or hyaline degeneration (hyperplasia, eosinophil). This degenerative change apparently results from the intracytoplasmic accumulation of secretory material.

Neoplasms of the nasal mucosa did not occur in exposed or control rats of either sex.

Kidney: Lipomas were observed in 2/50 male rats exposed to 300 ppm. The lipoma of the kidney is a benign mesenchymal neoplasm consisting of completely differentiated fat cells with interspersed fibrocytes, collagen, and blood vessels. The historical incidence of renal mesenchymal neoplasms in male F344/N rats is 0/346 for chamber controls and 2/1,590 (0.1%) for untreated controls; the highest observed incidence is 1/50.

Urinary Bladder: Papillomas of the transitional epithelium were observed in 2/49 male rats exposed to 300 ppm. The historical incidence of urinary bladder transitional epithelium neoplasms in male F344/N rats is 3/339 (0.9%) for chamber controls and 1/1,552 (0.1%) for untreated controls; no more than one neoplasm has been observed in any control group. Hyperplasia of the transitional epithelium was not observed in males; hyperplasia was seen in a single high concentration female rat.

TABLE 6. NUMBERS OF RATS WITH SELECTED LESIONS IN THE NASAL PASSAGE IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

Site/Lesion	Male			Female		
	Chamber Control	100 ppm	300 ppm	Chamber Control	100 ppm	300 ppm
Number examined	48	50	50	50	49	50
Olfactory epithelium						
Cyst	0	4	*6	0	*5	**13
Erosion	0	**8	1	0	3	4
Hyperplasia, eosinophil (a)	1	0	0	2	*9	**21
Metaplasia	0	*6	4	0	1	0
Respiratory epithelium						
Cyst	2	**13	*9	0	*6	**10
Hyperplasia	12	*24	**28	8	**19	**19

(a) Refers to hyperplasia of the olfactory epithelial cells that also have eosinophilic cytoplasm
*P<0.05 vs. controls
**P<0.01 vs. controls

FIFTEEN-DAY STUDIES

Three of five male mice exposed to 200 ppm died before the end of the studies (Table 7). Compound-related clinical signs seen at 200 ppm included lethargy and palpebral closure. Ataxia was seen at 100 ppm. There was no correlation between the exposure concentration and the change in mean body weights. The absolute and relative liver weights were increased for mice exposed to 200 ppm (Table I3). One control mouse and five mice of each sex exposed to 200 ppm were examined microscopically. Severe hyperemia and hemorrhage of the pulmonary parenchyma were seen in exposed male mice that died on day 3. Three other exposed male mice had interstitial pneumonia. Four of five male mice exposed to 200 ppm had moderate-to-severe necrosis of the liver; all five female mice exposed to 200 ppm had hyperplasia of the epithelium of the intrapulmonary bronchi and centrilobular hepatocellular necrosis, vacuolization, and polymorphonuclear leukocyte infiltrates in the liver.

THIRTEEN-WEEK STUDIES

The incidence of deaths was not related to the exposure concentrations (Table 8). The final mean body weights of mice exposed to 25, 60, or 160 ppm were 12%, 12%, or 20% lower than that of controls for males and 13%, 14%, or 16% lower for females. Lethargy was observed for mice exposed to 60 or 160 ppm; palpebral closure was observed for mice exposed to 160 ppm. The relative liver weights for exposed and control mice were not significantly different (Table I4). Inflammation of the lung was observed in 5/10 male and 3/9 female mice exposed to 160 ppm, in 4/9 male and 2/10 female mice exposed to 60 ppm, and in 1/10 female controls. Metaplasia of the respiratory epithelium of the nasal turbinates (hyaline cytoplasmic alteration) was seen in all exposed groups. Acute inflammation and/or metaplasia of the nasal turbinates were seen in 7/10 male and 9/9 female mice exposed to 160 ppm, 7/8 male and 10/10 female mice exposed to 60 ppm, 8/9 male and 9/10 female mice exposed to 25 ppm, 3/10 male and 4/10 female mice exposed to

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY INHALATION STUDIES OF VINYL TOLUENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams)			Necropsy Weight Relative to Controls (percent)
		Initial	Necropsy	Change (b)	
MALE					
0	5/5	24.0	26.4	+2.4	
10	5/5	27.0	27.8	+0.8	105
25	5/5	26.2	27.6	+1.4	105
50	5/5	26.2	26.0	−0.2	98
100	5/5	27.0	27.2	+0.2	103
200	(c) 2/5	26.4	26.5	+0.1	100
FEMALE					
0	5/5	22.6	24.8	+2.2	
10	5/5	21.2	23.6	+2.4	95
25	5/5	23.4	24.8	+1.4	100
50	5/5	21.6	22.6	+1.0	91
100	5/5	23.2	23.8	+0.6	96
200	5/5	22.4	23.6	+1.2	95

(a) Number surviving/number initially in group
(b) Mean body weight change of the group
(c) Day of death: 3,3,6

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF VINYL TOLUENE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Necropsy	Change (c)	Necropsy Weight Relative to Controls (percent)
MALE					
0	(d) 9/10	23.2 ± 0.4	33.1 ± 0.7	+9.8 ± 0.7	
10	(e) 5/10	22.6 ± 0.7	33.4 ± 1.1	+10.2 ± 1.0	101
25	10/10	22.4 ± 0.5	29.1 ± 0.5	+6.7 ± 0.2	88
60	(f) 4/10	22.9 ± 0.5	29.0 ± 0.4	+5.5 ± 0.3	88
160	(g) 8/10	23.3 ± 0.5	26.5 ± 0.5	+2.9 ± 0.5	80
FEMALE					
0	10/10	18.4 ± 0.2	27.6 ± 0.8	+9.2 ± 0.8	
10	(e) 8/10	17.5 ± 0.4	25.8 ± 0.6	+8.4 ± 0.5	93
25	10/10	17.7 ± 0.7	24.0 ± 0.4	+6.3 ± 0.5	87
60	10/10	17.2 ± 0.7	23.8 ± 0.4	+6.6 ± 0.6	86
160	10/10	16.9 ± 0.8	23.2 ± 0.3	+6.3 ± 0.7	84

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 4
(e) Killed after accidental overexposure during week 5
(f) Week of death: all 2
(g) Week of death: all 1

10 ppm, and 1/10 female controls. Lesions of the lungs and nasal turbinates were not seen in the male controls.

Dose Selection Rationale: Because of lower mean body weight gain of animals exposed to 25 ppm or more, lesions in the nasal passage, and lethargy at 60 ppm and higher, inhalation exposure concentrations selected for mice for the 2-year studies were 10 and 25 ppm vinyl toluene, 6 hours per day, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of mice exposed to 25 ppm were 10%-23% lower than those of controls after week 8; mean body weights of mice exposed to 10 ppm were 5%-14% lower than those of controls after week 37 for males and week 41 for females (Table 9 and Figure 5). No compound-related clinical signs were seen.

TABLE 9. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

Weeks on Study	Chamber Control		10 ppm			25 ppm		
	Av. Wt. (grams)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls)	Number of Survivors
MALE								
0	24.0	50	24.4	102	50	24.7	103	50
1	25.6	50	25.1	98	50	24.8	97	50
2	26.6	50	26.7	100	50	25.2	95	50
3	26.9	50	27.4	102	50	25.0	93	50
4	28.0	50	28.0	100	50	25.2	90	50
5	28.2	50	28.5	101	50	26.4	94	50
6	29.2	50	29.4	101	50	26.3	90	50
7	29.1	50	29.6	102	50	27.0	93	50
8	30.0	50	30.2	101	50	26.9	90	50
9	30.3	50	30.3	100	50	27.1	89	50
10	30.7	50	31.1	101	50	27.6	90	50
11	31.4	50	31.8	101	50	27.9	89	50
12	32.0	50	32.0	100	50	28.1	88	50
13	32.3	50	32.2	100	50	28.2	87	50
17	32.7	50	32.1	98	50	28.6	87	50
21	34.2	50	33.0	96	50	29.2	85	50
25	34.4	50	33.4	97	50	29.1	85	48
29	35.7	50	33.6	94	50	29.9	84	48
33	36.2	50	35.1	97	50	30.2	83	48
37	36.4	50	34.3	94	50	30.5	84	47
41	37.7	49	35.0	93	50	31.2	83	47
45	38.3	49	35.8	93	50	32.0	84	47
49	38.4	49	36.3	95	50	31.4	82	47
53	39.4	49	36.5	93	49	31.7	80	47
57	39.9	49	37.5	94	48	32.0	80	47
61	40.3	49	37.7	94	48	32.5	81	47
65	40.3	49	37.9	94	47	32.8	81	47
69	41.5	49	38.2	92	47	33.3	80	47
73	40.7	49	37.9	93	47	32.9	81	47
77	39.7	47	37.3	94	47	32.9	83	47
81	40.2	47	36.8	92	45	33.2	83	47
85	40.7	45	36.0	88	42	33.2	82	46
89	40.2	44	36.5	91	41	33.3	83	46
93	40.3	42	36.4	90	38	33.3	83	46
97	40.3	38	36.7	91	35	33.7	84	45
101	39.6	36	36.3	92	32	33.6	85	42
Mean for weeks								
1-13	29.3		29.4	100.3		26.6	90.1	
17-49	36.0		34.3	95.3		30.2	83.9	
53-101	40.2		37.1	92.3		33.0	82.1	
FEMALE								
0	18.7	50	19.1	102	50	18.9	101	50
1	20.0	50	19.8	99	50	20.0	100	49
2	21.3	50	21.6	101	50	20.3	95	49
3	22.8	50	22.1	97	50	21.0	92	49
4	23.2	50	22.8	98	50	21.1	91	49
5	23.6	50	23.2	98	50	21.5	91	49
6	24.2	50	23.5	97	50	21.9	90	48
7	24.2	49	24.6	102	50	22.3	92	48
8	24.9	49	24.5	98	50	22.1	89	48
9	25.8	49	25.4	98	50	22.8	88	48
10	26.0	49	25.9	100	50	22.6	87	48
11	26.5	49	26.3	99	50	23.1	87	48
12	26.9	49	26.4	98	50	23.3	87	48
13	26.4	49	26.4	100	50	23.6	89	48
17	27.2	49	26.5	97	50	23.7	87	48
21	28.8	49	27.6	96	50	24.4	85	48
25	28.5	49	28.0	98	50	24.7	87	42
29	29.9	49	27.7	93	50	25.2	84	42
33	31.1	49	29.4	95	50	26.0	84	42
37	30.1	49	29.0	96	50	26.1	87	42
41	31.2	49	28.7	92	50	26.2	84	42
45	31.1	49	29.6	95	50	26.6	86	42
49	32.0	49	29.6	93	50	26.9	84	42
53	33.4	49	29.5	88	50	26.8	80	41
57	32.9	49	29.9	91	50	27.0	82	41
61	33.6	49	30.1	90	50	26.9	80	41
65	32.9	49	30.4	92	50	27.2	83	41
69	34.8	48	31.0	89	49	27.4	79	40
73	34.7	48	31.0	89	49	27.3	79	40
77	35.2	48	30.9	88	49	27.4	78	40
81	35.6	47	30.8	87	49	27.7	78	40
85	35.9	45	30.4	85	48	27.7	77	40
89	35.8	45	30.8	86	47	27.7	77	38
93	35.3	45	30.0	85	47	27.8	79	38
97	35.2	44	30.8	88	45	27.9	79	35
101	34.8	40	31.3	90	39	28.2	81	35
Mean for weeks								
1-13	24.3		24.0	98.8		22.0	90.5	
17-49	30.0		28.5	95.0		25.5	85.0	
53-101	34.6		30.5	88.2		27.5	79.5	

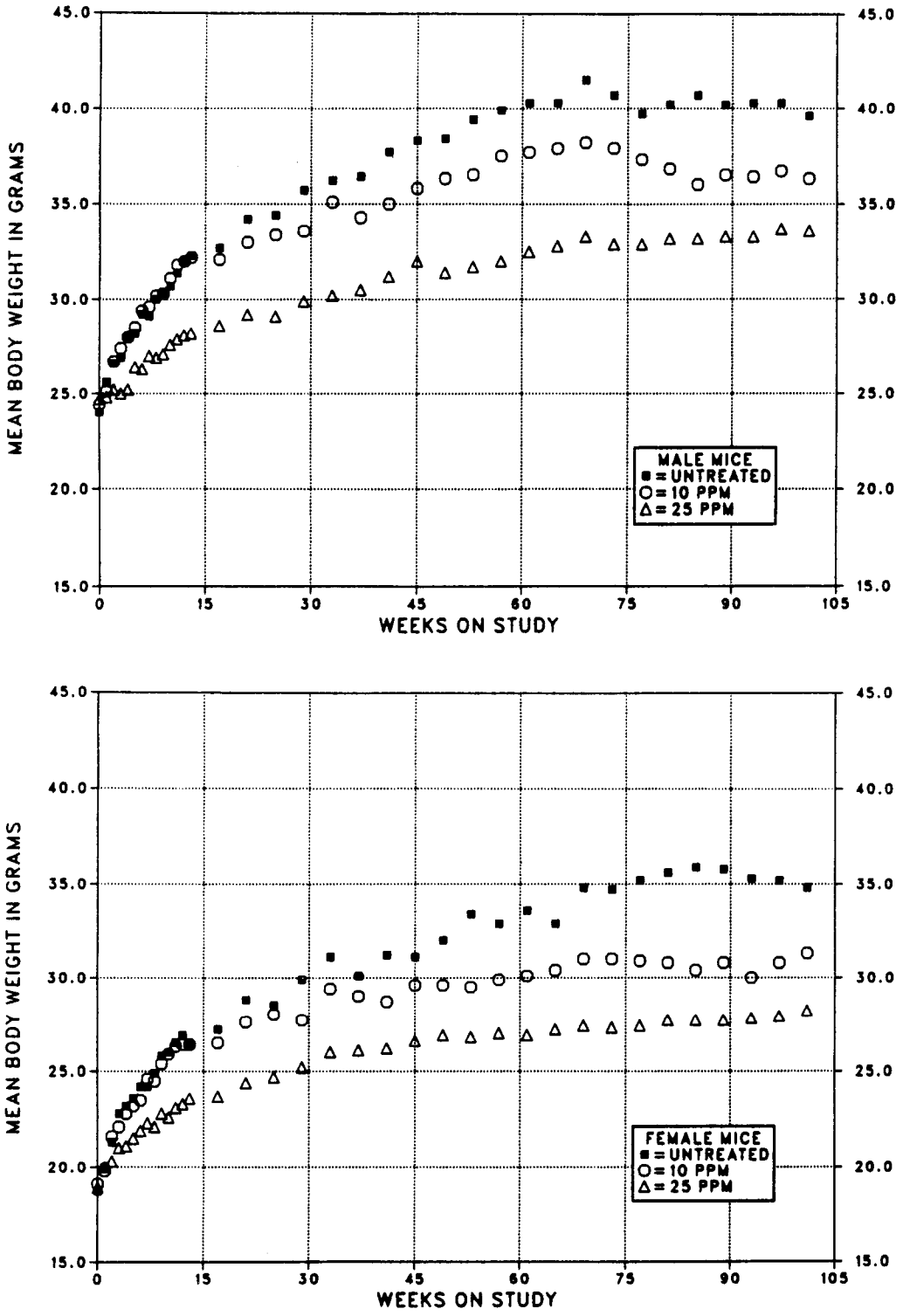

FIGURE 5. GROWTH CURVES FOR MICE EXPOSED TO VINYL TOLUENE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice exposed to vinyl toluene at the concentrations used in these studies and for controls are shown in Table 10 and in the Kaplan and Meier curves in Figure 6. During week 21, liquid vinyl toluene entered the 25-ppm chamber due to a technical error in the connection of the vinyl toluene vapor generation lines; two males and six females came into direct contact with the liquid and died or were killed in a moribund condition. The survival of male mice exposed to 25 ppm was significantly greater than that of controls after day 707. No other significant differences in survival were seen between any groups of either sex.

Pathology and Statistical Analyses of Results

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

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

TABLE 10. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

	Chamber Control	10 ppm	25 ppm
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	6	7	2
Moribund kills	10	13	4
Killed accidentally	1	0	3
Animals surviving to study termination	33	30	41
Mean survival (days)	694	679	691
Survival P values (b)	0.026	0.472	0.031
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	8	2	7
Moribund kills	6	10	1
Killed accidentally	0	1	8
Animals surviving to study termination	36	37	34
Mean survival (days)	698	712	611
Survival P values (b)	0.434	0.847	0.473

(a) First day of termination period: 731
(b) The result of the life table trend test is in the chamber control column, and the results of the life table pairwise comparisons with the chamber controls are in the dosed columns.

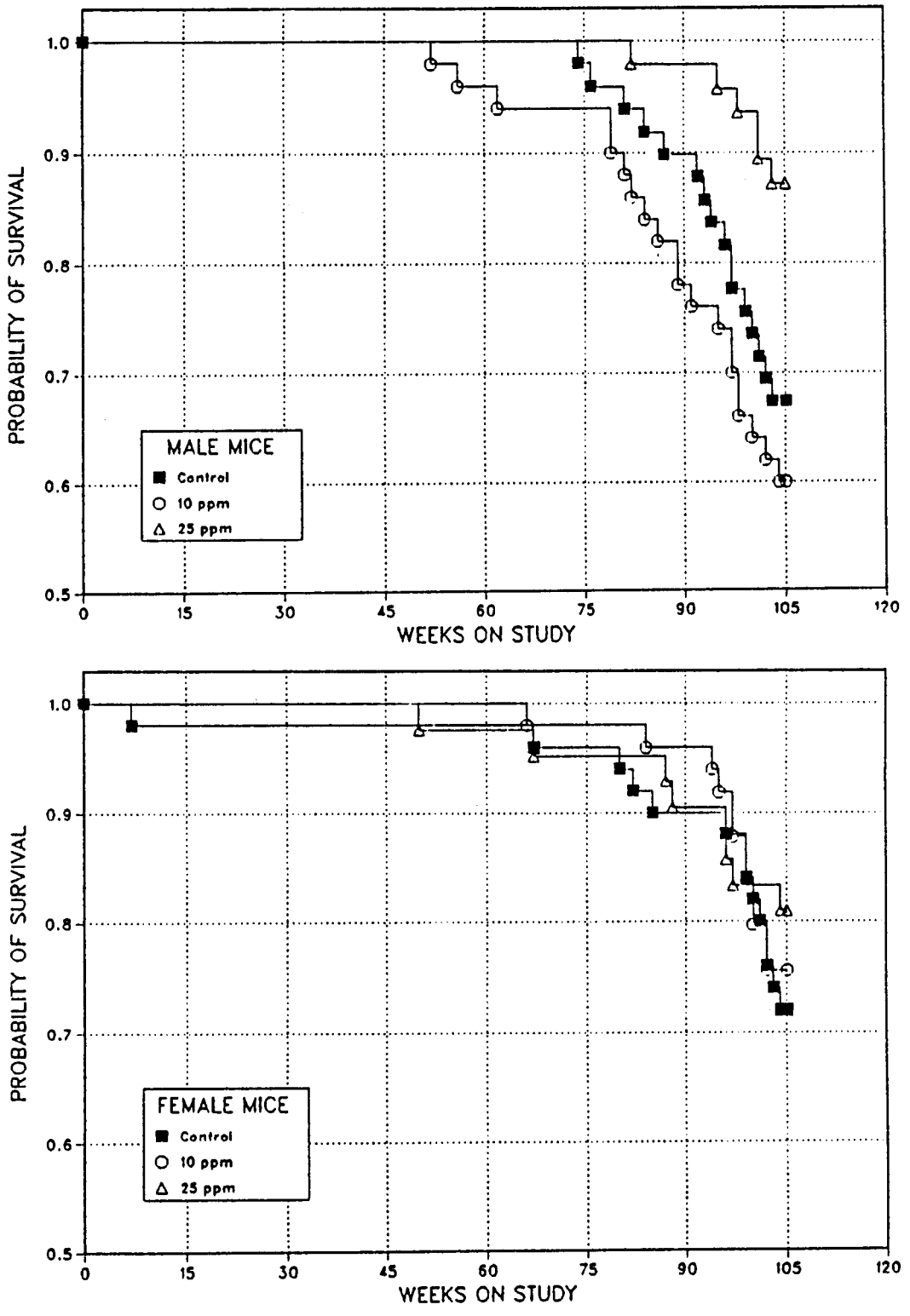

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO VINYL TOLUENE BY INHALATION FOR TWO YEARS

Nasal Passage: Increased incidences of chronic active inflammation and hyperplasia of the respiratory epithelium occurred in exposed mice (Table 11). Lesions were located in the middle and posterior portions of the dorsal meatus. The severity of the lesions was dose related; inflammation and hyperplasia were generally mild and moderate in the 10-ppm males and females, respectively, and moderate and marked in the 25-ppm males and females, respectively. Inflammation was characterized by focal infiltration of the mucosa by varying numbers of neutrophils and mononuclear cells. Hyperplasia consisted of increased height of the epithelium, downgrowth of ciliated columnar cells into the submucosal glands, formation of intraepithelial glandlike structures, and extension of the respiratory epithelium into areas usually covered by olfactory epithelium. Neoplasms of the nasal passage were not observed.

Lung: Chronic active inflammation of the bronchioles occurred at increased incidences in exposed mice (Table 11). The severity of the lesion was minimal to moderate and varied considerably within and among the exposure groups. It consisted of focal accumulations of neutrophils, macrophages, and lymphocytes within the walls of bronchioles and the interstitium of adjacent alveoli. The epithelium of affected alveoli had increased numbers of cuboidal cells; the lumina contained some inflammatory cells, proteinaceous material, and when severe, eosinophilic crystals and cholesterol clefts.

Alveolar/bronchiolar neoplasms occurred with a significant negative trend in male mice, and the incidences in the 25-ppm group were significantly lower than those in controls (Table 12).

Hematopoietic System: Lymphomas in males occurred with a significant negative trend; the incidence in the group exposed to 25 ppm was significantly lower than that in the controls (Table 13). A marginal ($P<0.10$) decrease was also observed for exposed females (chamber control, 16/48; low dose, 9/49; high dose, 8/50).

Liver: The incidences of hepatocellular carcinomas and adenomas or carcinomas (combined) in the female group exposed to 25 ppm were significantly lower than those in controls (Table 14).

TABLE 11. NUMBERS OF MICE WITH SELECTED RESPIRATORY TRACT LESIONS IN THE TWO-YEAR INHALATION STUDIES OF VINYL TOLUENE

Site/Lesion	Male			Female		
	Chamber Control	10 ppm	25 ppm	Chamber Control	10 ppm	25 ppm
Number examined (a)	50	48	49	48	49	48
Nasal passage						
Chronic active inflammation	2	**47	**48	3	**49	**47
Respiratory epithelium						
Hyperplasia	5	**48	**49	5	**49	**47
Lung/bronchiole						
Chronic active inflammation	0	**(b) 15	**30	0	**14	**(b) 37

(a) Unless otherwise specified
(b) Forty-nine mice were examined.
**$P<0.01$ vs. controls

TABLE 12. ALVEOLAR/BRONCHIOLAR NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (a)

	Chamber Control	10 ppm	25 ppm (b)
Adenoma			
Overall Rates	9/50 (18%)	2/49 (4%)	2/49 (4%)
Terminal Rates	6/33 (18%)	2/30 (7%)	2/41 (5%)
Day of First Observation	687	731	731
Logistic Regression Tests	P=0.011N	P=0.037N	P=0.018N
Carcinoma			
Overall Rates	3/50 (6%)	3/49 (6%)	0/49 (0%)
Adenoma or Carcinoma (c)			
Overall Rates	12/50 (24%)	5/49 (10%)	2/49 (4%)
Terminal Rates	8/33 (24%)	4/30 (13%)	2/41 (5%)
Day of First Observation	687	358	731
Logistic Regression Tests	P=0.003N	P=0.065N	P=0.003N

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Two males died or were killed at week 21 after coming into direct contact with liquid vinyl toluene that entered the chamber.
(c) Historical incidence in chamber controls in NTP studies (mean ± SD): 82/398 (21% ± 8%); historical incidence in untreated controls in NTP studies: 277/1,684 (16% ± 7%)

TABLE 13. HEMATOPOIETIC SYSTEM NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (a)

	Chamber Control	10 ppm	25 ppm (b)
Lymphoma (c)			
Overall Rates	7/50 (14%)	3/50 (6%)	0/50 (0%)
Terminal Rates	6/33 (18%)	2/30 (7%)	0/41 (0%)
Day of First Observation	670	632	
Life Table Tests	P=0.003N	P=0.203N	P=0.004N
Logistic Regression Tests	P=0.005N	P=0.186N	P=0.006N

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Two males died or were killed at week 21 after coming into direct contact with liquid vinyl toluene that entered the chamber.
(c) Historical incidence of lymphomas or leukemia (combined) in chamber controls in NTP studies (mean ± SD): 33/398 (8% ± 3%); historical incidence in untreated controls in NTP studies: 196/1,692 (12% ± 6%)

TABLE 14. HEPATOCELLULAR NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (a)

	Chamber Control	10 ppm	25 ppm (b)
Adenoma			
Overall Rates	4/48 (8%)	(c) 2/16 (13%)	2/49 (4%)
Carcinoma			
Overall Rates	6/48 (13%)	(c) 3/16 (19%)	0/49 (0%)
Terminal Rates	4/36 (11%)		0/34 (0%)
Day of First Observation	692		
Logistic Regression Test			P=0.026N
Adenoma or Carcinoma (d)			
Overall Rates	9/48 (19%)	(c) 5/16 (31%)	2/49 (4%)
Terminal Rates	7/36 (19%)		1/34 (3%)
Day of First Observation	692		42
Logistic Regression Test			P=0.021N

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Six females died or were killed at week 21 after coming into direct contact with liquid vinyl toluene that entered the chamber.
(c) Incomplete sampling of tissues for low concentration group for nontarget tissues
(d) Historical incidence in chamber controls in NTP studies (mean ± SD): 34/397 (9% ± 3%); historical incidence in untreated controls in NTP studies: 163/1,683 (10% ± 4%)

Vinyl toluene did not induce gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a preincubation protocol at doses up to 1,000 µg/plate with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Zeiger et al., 1987; Table H1). In the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells, vinyl toluene gave a positive response in two trials conducted without S9 at the highest doses tested; these doses also produced severe toxicity, as evidenced by a relative total growth of less than 10% (McGregor et al., 1988; Table H2). Vinyl toluene was not tested in the mouse lymphoma assay with S9. In cytogenetic tests with Chinese hamster ovary cells, vinyl toluene did not induce sister chromatid exchanges or chromosomal aberrations in either the presence or the absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table H3). The methodology and full results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

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Inhalation studies of the toxicity and carcinogenicity of vinyl toluene were conducted in F344/N rats and B6C3F$_1$ mice of each sex. For the 2-year studies, groups of 50 rats of each sex were exposed to vinyl toluene for 6 hours per day, 5 days per week for 103 weeks at concentrations of 0, 100, or 300 ppm; groups of mice were exposed under similar conditions to 0, 10, or 25 ppm. For both rats and mice, concentration selection for the 2-year studies was based primarily on body weight effects, lethargy, and toxic lesions of the nasal passage observed in the 15-day and 13-week studies.

The mice were approximately 10 times more sensitive to inhalation of vinyl toluene than were the rats in the current studies. Intraperitoneal injections of vinyl toluene show that mice are also more sensitive by that route, experiencing a more pronounced reduction in hepatic glutathione content than do rats (Heinonen and Vainio, 1980). Injection did not affect hepatic P450 enzymes in rats but caused profound depression in mice. Mice clearly are more sensitive to the toxic effects of vinyl toluene than are rats, but the exact mechanisms that account for this species difference are not known.

Throughout the 2-year studies, body weights of rats exposed to 300 ppm vinyl toluene averaged 4%-11% lower than those of controls. No significant differences in survival were seen in any groups of rats of either sex. The lowered body weights and the chemically related lesions occurring in the nasal passage indicated that the concentrations were adequate for assessing the long-term toxicity and carcinogenicity of vinyl toluene and that higher doses would not have been appropriate.

In rats, the most striking change in the nasal passage was a loss of olfactory epithelium with replacement by respiratory epithelium. This change was most prominent in the most anterior extension of the olfactory epithelium along the dorsal meatus, where exposure to the chemical may be highest. The Bowman's glands beneath the olfactory epithelium also were often replaced by ciliated columnar cells similar to the respiratory epithelium. These changes have been seen with other toxic chemicals, such as methyl isocyanate (Boorman et al., 1987), dimethylamine (Buckley et al., 1985), and chlorine (Jiang et al., 1986), and may represent an adaptive response of the olfactory epithelium. There was a mild diffuse hyperplasia of the respiratory epithelium, which is often seen in association with an inflammatory response. Focal proliferative lesions or neoplasms of the nasal passage were not found in rats.

Transitional cell papillomas of the urinary bladder were seen in two male rats exposed to 300 ppm but were not considered to be related to vinyl toluene exposure. Hyperplastic lesions of the urinary bladder were not found in any animals. Neoplasms of the urinary bladder were not found in female rats, but one high concentration female had focal hyperplasia of the urinary bladder. The renal pelvis is lined by transitional epithelium similar to that which lines the urinary bladder; hyperplasia of the renal pelvic transitional epithelium was found in two control males and three high concentration females. Although transitional epithelial neoplasms of the urinary bladder are uncommon, the historical incidence of this neoplasm in chamber control male F344/N rats at the study laboratory is 3/339 (0.9%). The two neoplasms in the high concentration males were considered to be unrelated to vinyl toluene exposure because of the low number and lack of supporting evidence of hyperplasia.

Three mesenchymal renal neoplasms were found in the 300-ppm male rats. Two of these were diagnosed as lipomas and were considered to be of interstitial cell origin, a lipid-containing renal cell associated with aldosterone and electrolyte balance (Kriz and Kaissling, 1985). This neoplasm is uncommon in F344/N rats and has not been well described. Chemically induced neoplasms of the kidney are almost invariably derived from the epithelium of the nephron; some potent carcinogens induce nephroblastomalike neoplasms or anaplastic mesenchymal neoplasms (Hard, 1976). No chemicals have been associated with the induction of lipomas, and the occurrence of this neoplasm in two high concentration male rats is considered spurious and unrelated to the administration of vinyl toluene. The third renal mesenchymal neoplasm was a sarcoma that contained marked osseous metaplasia. This neoplasm was considered unrelated

to the interstitial cell neoplasms (lipomas) or to vinyl toluene exposure.

During most of the 2-year studies, the body weights of mice exposed to 25 ppm vinyl toluene averaged 10%-23% lower than those of control mice, indicating that a higher exposure concentration could not have been tolerated even though there was no decreased survival in the exposed animals.

The lesions of the nasal passage in mice were analogous to those found in rats, with extension of respiratory epithelium into areas normally covered by olfactory epithelium. This may represent metaplasia of olfactory epithelium to ciliated cells similar in appearance to respiratory epithelium or loss of olfactory epithelium, with extension of the respiratory epithelium into areas of olfactory epithelium. This change was diagnosed as respiratory epithelial hyperplasia. As in the rats, ciliated cells extended down into and replaced the cells of Bowman's glands. There also appeared to be some atrophy of the nerves in the submucosa of the nasal passage, a lesion not recognized in rats. No primary neoplasms were seen in the nasal passage in mice.

Negative trends in the incidences of neoplasms were associated with vinyl toluene exposure in mice. Malignant lymphomas showed a marked decline in males and a marginally significant decrease in females. Pulmonary neoplasms were markedly decreased in males, but no difference was seen in females. Female mice also showed a marginal decline in hepatocellular neoplasms. The mice in these studies showed weight reduction associated with vinyl toluene exposure which may have been due to toxicity or reduced feed consumption. A decrease in neoplasms has been seen in rodents with reduced feed consumption (Zurcher et al., 1982), but the reason for the negative neoplasm trends in the current studies is not known.

Exposure to 300 ppm vinyl toluene previously resulted in a borderline experimental neuropathy in rats (Gagnaire et al., 1986). In a 21-week inhalation study, the animals did not show signs of neurotoxicity, and no structural changes were seen in teased nerve fiber preparations or by electron microscopy. However, temporary decreases in sensory and motor nerve conduction velocity were found in the tail of rats exposed to vinyl toluene for 15-20 weeks. In another study, a slight decrease in motor nerve conduction velocity was seen after exposure to 100 ppm for 12 weeks (Seppalainen and Savolainen, 1982a,b). No clinical or histologic evidence of nerve damage was seen after 2 years, suggesting that these changes were indeed borderline.

Epoxide intermediates are possibly formed by the metabolism of vinyl toluene (Heinonen and Vainio, 1980), and it has been suggested that the main reactive intermediate is vinyl toluene-7,8-oxide (Heinonen, 1984). Because of their electrophilic character, the intermediates could bind to nucleic acids and proteins, leading to toxicity, mutagenicity, and carcinogenicity. In the current studies, there was moderate evidence of toxicity and vinyl toluene was mutagenic in cultured mammalian cells, but there was no evidence of carcinogenicity. The reason for the lack of carcinogenicity is unknown, but given the toxicity seen in the nasal passage and the body weight losses, it is unlikely that the rats or mice could have tolerated much higher concentrations.

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

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** for male or female F344/N rats exposed to 100 or 300 ppm vinyl toluene and *no evidence of carcinogenic activity* for male or female B6C3F$_1$ mice exposed to 10 or 25 ppm.

There was evidence of chemical-related toxicity to the nasal passage in both rats and mice.

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

V. REFERENCES

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APPENDIX A

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

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

	Chamber Control	100 ppm	300 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	24	29	28
Natural death	6	4	3
Survivors			
Terminal sacrifice	19	17	19
Wrong sex	1		
Animals examined microscopically	49	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(43)	(9)	(47)
Intestine large, colon	(46)	(13)	(49)
Serosa, carcinoma, metastatic, intestine small	1 (2%)		
Intestine small, ileum	(44)	(12)	(44)
Jejunum, adenocarcinoma, mucinous			1 (2%)
Intestine small, jejunum	(45)	(13)	(47)
Adenocarcinoma	1 (2%)		
Liver	(49)	(42)	(50)
Fibrosarcoma, metastatic	1 (2%)		
Neoplastic nodule	2 (4%)	2 (5%)	1 (2%)
Mesentery	(8)	(4)	(6)
Fat, adenocarcinoma, metastatic, intestine small	1 (13%)		
Pancreas	(46)	(19)	(49)
Pharynx	(1)	(1)	(1)
Palate, papilloma squamous	1 (100%)	1 (100%)	
Salivary glands	(48)	(18)	(50)
Fibrosarcoma		1 (6%)	
Stomach, forestomach	(48)	(13)	(49)
Stomach, glandular	(47)	(14)	(50)
CARDIOVASCULAR SYSTEM			
Heart	(49)	(14)	(50)
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(24)	(50)
Adrenal gland, cortex	(49)	(20)	(50)
Adenoma	2 (4%)		
Carcinoma			1 (2%)
Adrenal gland, medulla	(49)	(21)	(46)
Pheochromocytoma malignant	1 (2%)	3 (14%)	2 (4%)
Pheochromocytoma complex	3 (6%)		1 (2%)
Pheochromocytoma benign	11 (22%)	6 (29%)	11 (24%)
Pheochromocytoma benign, multiple	3 (6%)		3 (7%)
Islets, pancreatic	(46)	(16)	(49)
Adenoma	5 (11%)	3 (19%)	5 (10%)
Adenoma, two	1 (2%)		
Carcinoma			1 (2%)
Parathyroid gland	(45)	(14)	(45)
Adenoma	1 (2%)		
Pituitary gland	(49)	(35)	(50)
Pars distalis, adenoma	27 (55%)	20 (57%)	28 (56%)
Pars distalis, adenoma, multiple	1 (2%)		1 (2%)
Pars distalis, adenoma, two	3 (6%)	1 (3%)	1 (2%)
Pars distalis, carcinoma	3 (6%)	1 (3%)	1 (2%)

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

	Chamber Control	100 ppm	300 ppm
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(49)	(20)	(50)
Bilateral, C-cell, adenoma			1 (2%)
C-cell, adenoma	7 (14%)	2 (10%)	6 (12%)
C-cell, carcinoma	1 (2%)	1 (5%)	1 (2%)
Follicular cell, carcinoma		2 (10%)	1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS	(1)		(1)
Lipoma	1 (100%)		
GENITAL SYSTEM			
Epididymis	(47)	(16)	(50)
Preputial gland	(46)	(18)	(48)
Adenoma	1 (2%)		2 (4%)
Carcinoma	1 (2%)	2 (11%)	1 (2%)
Prostate	(49)	(18)	(49)
Adenoma	1 (2%)		
Seminal vesicle	(41)	(13)	(43)
Adenocarcinoma, metastatic, intestine small	1 (2%)		
Testes	(49)	(42)	(50)
Bilateral, interstitial cell, adenoma	25 (51%)	21 (50%)	33 (66%)
Interstitial cell, adenoma	10 (20%)	10 (24%)	8 (16%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(48)	(15)	(50)
Lymph node	(49)	(27)	(50)
Inguinal, renal, adenocarcinoma, metastatic, intestine small	1 (2%)		
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland		1 (4%)	
Lymph node, mandibular	(44)	(14)	(48)
Carcinoma, metastatic, thyroid gland	1 (2%)		
Lymph node, mesenteric	(44)	(17)	(48)
Spleen	(49)	(35)	(49)
Thymus	(38)	(14)	(38)
Thymoma malignant			1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(38)	(20)	(46)
Adenocarcinoma		1 (5%)	1 (2%)
Fibroadenoma	1 (3%)		1 (2%)
Skin	(49)	(23)	(50)
Basosquamous tumor benign		1 (4%)	
Keratoacanthoma	2 (4%)	3 (13%)	5 (10%)
Keratoacanthoma, two		1 (4%)	
Papilloma squamous	1 (2%)		1 (2%)
Trichoepithelioma			1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	1 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	3 (6%)	1 (4%)	1 (2%)
Subcutaneous tissue, neurofibroma			1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)	1 (4%)	
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(2)	(4)	(1)
Hindlimb, rhabdomyosarcoma		1 (25%)	
Intercostal, fibroma		1 (25%)	

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

	Chamber Control	100 ppm	300 ppm
NERVOUS SYSTEM			
Brain	(49)	(15)	(50)
Astrocytoma, NOS	1 (2%)		
Carcinoma, early invasion	1 (2%)		
Carcinoma, metastatic, pituitary gland	1 (2%)		
RESPIRATORY SYSTEM			
Larynx	(37)	(5)	(41)
Carcinoma, metastatic, thyroid gland	1 (3%)		
Lung	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma		1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)		1 (2%)
Fibrosarcoma, metastatic	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland		1 (2%)	
Pheochromocytoma complex, metastatic	1 (2%)		
Trachea	(48)	(14)	(50)
Carcinoma, metastatic, thyroid gland	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland		(1)	
Right, carcinoma		1 (100%)	
URINARY SYSTEM			
Kidney	(49)	(35)	(50)
Lipoma			2 (4%)
Sarcoma			1 (2%)
Urinary bladder	(48)	(12)	(49)
Transitional epithelium, papilloma			2 (4%)
SYSTEMIC LESIONS			
Multiple organs	*(49)	*(50)	*(50)
Leukemia mononuclear	25 (51%)	26 (52%)	20 (40%)
Mesothelioma benign			1 (2%)
Mesothelioma malignant	3 (6%)	1 (2%)	
TUMOR SUMMARY			
Total animals with primary neoplasms **	48	50	50
Total primary neoplasms	152	116	149
Total animals with benign neoplasms	48	45	49
Total benign neoplasms	108	73	116
Total animals with malignant neoplasms	38	37	29
Total malignant neoplasms	43	43	34
Total animals with secondary neoplasms ***	5	1	1
Total secondary neoplasms	12	2	1
Total animals with neoplasms-- uncertain benign or malignant	1		
Total uncertain neoplasms	1		

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

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

DAYS ON STUDY	057	371	422	492	506	511	511	520	525	532	553	557	599	607	613	621	623	623	633	638	643	647	652	658	673
CARCASS ID	06111	06911	07311	09511	05551	06661	07011	06011	08911	08221	08881	08861	08711	07661	07711	06411	06651	08331	05411	05991	07991	09711	07441	08441	07881
ALIMENTARY SYSTEM																									
Esophagus		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large		+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum		M	+		+	+	M	+		+	+	+	+	M	+		+	+	+	+	+	+	+	+	+
Intestine large, colon		+	+		+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Serosa, carcinoma, metastatic, intestine small																									
Intestine large, rectum		M	+		M	+	M	M		M	+	+	+	M	M		+	+	+	M	+	+	+	+	M
Intestine small		+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum		M	+		+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Intestine small, ileum		M	+		+	+	+	+		+	+	+	+	+	+		+	+	+	A	+	+	+	+	+
Intestine small, jejunum		+	+		+	+	+	+		+	+	+	+	+	+		+	+	+	A	+	+	+	+	+
Adenocarcinoma																									
Liver		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																						X			
Neoplastic nodule																									
Mesentery																						+	+		
Fat, adenocarcinoma, metastatic, intestine small																									
Pancreas		M	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Palate, papilloma squamous																									
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach		+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Tooth						+																			
CARDIOVASCULAR SYSTEM																									
Heart		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																X									
Pheochromocytoma benign																	X	X	X	X		X			
Pheochromocytoma benign, multiple																									
Islets, pancreatic		M	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, two																									
Parathyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+	+
Adenoma																									
Pituitary gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X	X		X	X	X		X	X	X	X	X							X
Pars distalis, adenoma, multiple																									
Pars distalis, adenoma, two																									
Pars distalis, carcinoma													X												
Thyroid gland		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			X
C-cell, carcinoma																	X								
GENERAL BODY SYSTEM																									
Tissue, NOS																									
Lipoma																									
GENITAL SYSTEM																									
Epididymis		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Preputial gland		+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma																									
Prostate		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle		+	M	M	M	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine small																									
Testes		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X		X				X	X		X							X			X	X		X	
Interstitial cell, adenoma				X							X				X					X				X		

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

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

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

DAYS ON STUDY	6 8 3	6 9 3	6 9 7	7 0 0	7 1 4	7 2 1	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	TOTAL:
CARCASS ID	0 0 6 3 1	0 0 9 4 1	0 0 9 9 1	0 0 6 8 1	0 0 6 2 1	0 0 9 6 1	0 0 5 2 1	0 0 5 3 1	0 0 5 6 1	0 0 5 7 1	0 0 5 1 1	0 0 5 8 1	0 0 6 7 1	0 0 7 1 1	0 0 7 2 1	0 0 8 0 1	0 0 8 1 1	0 0 9 1 1	0 0 9 2 1	0 0 9 3 1	0 0 7 5 1	0 0 8 5 1	0 0 9 0 1	0 0 9 8 1	1 0 0 1	TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Serosa, carcinoma, metastatic, intestine small																				X						1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	36
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Adenocarcinoma																				X						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Fibrosarcoma, metastatic																										
Neoplastic nodule												X									X				
Mesentery	+	+			+									+						+					+	
Fat, adenocarcinoma, metastatic, intestine small																				X						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Pharynx	+																									
Palate, papilloma squamous	X																									
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Tooth												+														
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Adenoma											X									X						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4
Pheochromocytoma malignant												X														
Pheochromocytoma complex			X																X							
Pheochromocytoma benign			X							X						X	X	X		X						11
Pheochromocytoma benign, multiple						X			X												X					3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma			X	X								X	X	X												5
Adenoma, two											X															1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma					X																					1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X				X	X	X	X	X			X				X	X	X	X	X		X	X	27
Pars distalis, adenoma, multiple																							X			1
Pars distalis, adenoma, two													X		X		X									3
Pars distalis, carcinoma				X				X																		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X			X	X					X				X											7
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
Tissue, NOS							+																			1
Lipoma							X																			1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Carcinoma																				X						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Seminal vesicle	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenocarcinoma, metastatic, intestine small																				X						1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X			X	X		X			X	X	X	X	X	X		X			X		X	X	X	25
Interstitial cell, adenoma							X		X	X										X		X				10

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

DAYS ON STUDY	057	371	422	492	506	511	511	520	525	532	553	557	599	607	613	621	623	623	633	638	643	647	652	658	673
CARCASS ID	06111	06911	07311	09551	05551	06661	07011	06001	08911	08211	08811	08611	08711	07611	07711	06411	06511	08311	05411	05591	07911	09711	07411	08411	07811
HEMATOPOIETIC SYSTEM																									
Bone marrow		+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, renal, adenocarcinoma, metastatic, intestine small																									
Lymph node, mandibular		+	+	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																	X								
Lymph node, mesenteric		M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus		+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	M	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland		M	M	M	+	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	M	M	+	+	+
Fibroadenoma																								X	
Skin		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																				X					
Papilloma squamous					X																				
Subcutaneous tissue, fibroma													X												
Subcutaneous tissue, fibrosarcoma																						X			
Subcutaneous tissue, sarcoma																					X				
MUSCULOSKELETAL SYSTEM																									
Bone		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																		+			
NERVOUS SYSTEM																									
Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma, NOS								X																	
Carcinoma, early invasion																									
Carcinoma, metastatic, pituitary gland																									
RESPIRATORY SYSTEM																									
Larynx		M	M	M	M	M	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Carcinoma, metastatic, thyroid gland																	X								
Lung		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																	X								
Fibrosarcoma, metastatic																						X			
Pheochromocytoma complex, metastatic																X									
Nose		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Carcinoma, metastatic, thyroid gland																	X								
SPECIAL SENSES SYSTEM																									
Eye						+													+						
URINARY SYSTEM																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X					X	X		X	X				X	X	X			X	X	X
Mesothelioma malignant				X					X													X			

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

DAYS ON STUDY	6 8 3	6 9 3	6 9 7	7 0 0	7 1 4	7 2 1	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	TOTAL:
CARCASS ID	0 6 3 1	0 9 4 1	0 9 9 1	0 6 8 1	0 6 2 1	0 9 6 1	0 5 2 1	0 5 3 1	0 5 6 1	0 5 7 1	0 5 1 1	0 5 8 1	0 6 7 1	0 7 1 1	0 7 2 1	0 8 0 1	0 8 1 1	0 9 1 1	0 9 2 1	0 9 3 1	0 7 5 1	0 8 5 1	0 9 0 1	0 9 8 1	1 0 0 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Inguinal, renal, adenocarcinoma, metastatic, intestine small																				X					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, metastatic, thyroid gland																									1
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	38
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	38
Fibroadenoma																									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																							X		2
Papilloma squamous																									1
Subcutaneous tissue, fibroma																						X			2
Subcutaneous tissue, fibrosarcoma																		X					X		3
Subcutaneous tissue, sarcoma																									1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																									2
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma, NOS																									1
Carcinoma, early invasion				X																					1
Carcinoma, metastatic, pituitary gland								X																	1
RESPIRATORY SYSTEM																									
Larynx	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Carcinoma, metastatic, thyroid gland																									1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, thyroid gland																									1
Fibrosarcoma, metastatic																									1
Pheochromocytoma complex, metastatic																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, thyroid gland																									1
SPECIAL SENSES SYSTEM																									
Eye	+																								3
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	48
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear	X	X	X		X	X				X					X	X				X		X	X	X	X	25
Mesothelioma malignant																									3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 100 ppm

DAYS ON STUDY	3 9 3	4 6 5	4 7 9	4 8 4	4 9 9	5 1 9	5 3 3	5 3 9	5 3 9	5 5 4	5 5 4	5 8 3	5 9 3	6 1 1	6 1 3	6 2 3	6 2 4	6 2 7	6 3 3	6 3 7	6 5 8	6 6 0	6 6 6	6 8 0	6 8 7
CARCASS ID	2 8 1 1	2 8 6 1	2 7 9 1	2 5 9 1	2 8 9 1	2 9 3 1	2 5 4 1	2 6 1 1	2 6 7 1	2 5 8 1	2 7 1 1	2 7 3 1	2 8 2 1	2 8 3 1	2 9 1 1	2 9 9 8 1	2 6 6 5 1	2 9 6 1	2 5 3 1	2 7 7 1	2 7 7 8 1	2 6 6 0 1	2 9 9 0 1	2 7 7 0 1	2 7 7 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+													
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+													
Intestine large, cecum	+	A	M	M	M	+	M	+	A	+	+	+													
Intestine large, colon	+	A	+	+	+	+	+	+	A	+	+	+													
Intestine large, rectum	+	A	+	+	+	+	+	M	A	+	+	+													
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+													+
Intestine small, duodenum	+	A	+	+	+	+	+	+	A	+	+	+													+
Intestine small, ileum	M	A	+	+	+	+	+	+	A	+	+	+													
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	+													
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Neoplastic nodule																		X							
Mesentery																									
Pancreas	+	A	+	M	+	+	+	+	+	+	+	+		+						+					
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+							+						
Fibrosarcoma								X																	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+													
Stomach, forestomach	+	A	+	+	+	M	+	+	+	+	+	+													
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+													
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	M	+	+	+	+	+	+	+	+	+	+													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+								+				+	+
Adrenal gland, cortex	+	A	+	+	+	+	+	+	+	+	+	+												+	+
Adrenal gland, medulla	+	A	+	+	+	+	+	+	+	+	+	+								+				+	M
Pheochromocytoma malignant																				X					
Pheochromocytoma benign	X		X	X																				X	
Islets, pancreatic	+	A	+	M	+	+	+	+	+	+	+	+													
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+													
Pituitary gland	+	A	+	+	+	+	+	+	+	+	+	+			+						+		+	+	+
Pars distalis, adenoma					X			X	X	X	X	X									X		X	X	X
Pars distalis, adenoma, two																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	M	+								+					
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	M				+									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+													+
Carcinoma																									
Prostate	+	+	M	+	+	+	+	+	+	+	+	+					+			+			+		
Seminal vesicle	+	M	M	M		M	M	M	M	+	+	+					+			+			+		
Testes	+	+	+	+	+	+	+	+		+	+	M				+	+	+	+	+		+	+	+	+
Bilateral, interstitial cell, adenoma							X									X				X		X	X	X	
Interstitial cell, adenoma				X	X												X	X	X						
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+		+	+				+	+		+			
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland																				X					
Lymph node, mandibular	M	A	M	M	M	+	+	+	+	+	+	+							+			+			
Lymph node, mesenteric	+	A	M	+	+	+	+	+	+	+	+	+			+				M						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+			+	+	+	
Thymus	M	M	+	+	+	+	+	M	M	+	+	+							+						

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	687	689	694	695	697	697	700	714	728	728	728	728	728	729	729	729	729	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	28851	26631	28881	25551	25571	26661	29291	27411	25661	26441	26881	26991	27211	25111	25221	26221	28441	27661	28001	28711	29441	29551	29771	29991	30001	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus										+		+	+													15
Intestine large										+		+	+													15
Intestine large, cecum										+		+	+													9
Intestine large, colon										+		+	+													13
Intestine large, rectum										+		+	+													12
Intestine small										+		+	+													16
Intestine small, duodenum										+		+	+													14
Intestine small, ileum										+		+	+													12
Intestine small, jejunum										+		+	+													13
Liver	+	+	+	+		+		+	+	+		+	+		+		+	+		+	+	+	+		+	42
Neoplastic nodule									X																	2
Mesentery	+	+					+															+				4
Pancreas						+	+					+	+					+		+			+			19
Pharynx																								+		1
Palate, papilloma squamous																								X		1
Salivary glands	+						+			+		+				+										18
Fibrosarcoma																										1
Stomach										+		+	+													15
Stomach, forestomach										+		+	+													13
Stomach, glandular										+		+	+													14
Tooth							+		+	+																3
CARDIOVASCULAR SYSTEM																										
Heart										+		+	+													14
ENDOCRINE SYSTEM																										
Adrenal gland	+								+	+		+	+						+	+	+			+		24
Adrenal gland, cortex	+									+		+	+						+		+			+		20
Adrenal gland, medulla	+								+	+			+						+	+	+			+		21
Pheochromocytoma malignant									X												X					3
Pheochromocytoma benign																				X	X					6
Islets, pancreatic						+	+					+	+							+			+			16
Adenoma							X													X			X			3
Parathyroid gland										+		+	+													14
Pituitary gland	+	+	+	+	+		+	+	+	+		+	+	+	+	+		+		+		+	+	+		35
Pars distalis, adenoma					X		X	X	X	X		X		X						X		X		X		20
Pars distalis, adenoma, two																							X			1
Pars distalis, carcinoma				X																						1
Thyroid gland	+				+					+		+	+								+		+	+		20
C-cell, adenoma										X											X					2
C-cell, carcinoma																								X		1
Follicular cell, carcinoma													X										X			2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis							+			+		+	+													16
Preputial gland										+		+	+				+		+							18
Carcinoma													X						X							2
Prostate			+						+	+			+													18
Seminal vesicle			+							+		+	+		+									+		13
Testes	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		42
Bilateral, interstitial cell, adenoma	X	X	X		X			X					X		X	X	X	X	X			X	X	X	X		21
Interstitial cell, adenoma						X			X	X	X									X							10
HEMATOPOIETIC SYSTEM																										
Bone marrow										+		+	+				+									15
Lymph node	+	+			+	+	+			+		+	+				+	+								27
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland																										1
Lymph node, mandibular	+						+			+		+						+								14
Lymph node, mesenteric	+				+							+	+				+	+								17
Spleen	+	+	+			+				+	+	+	+			+	+	+			+	+	+			35
Thymus	+				+					+		+	+													14

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	393	465	479	484	499	519	533	539	539	554	554	583	593	611	613	623	624	627	633	637	658	660	666	680	687
CARCASS ID	28111	28611	27911	25911	28911	29311	25411	26111	26711	25811	27111	27311	28211	28311	29111	29811	26511	29611	25311	27711	27811	26011	29011	27011	27511
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	M	+	+	+	+	+	+	+	+													
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+										+			
Basosquamous tumor benign																									
Keratoacanthoma			X																						
Keratoacanthoma, two																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+													
Skeletal muscle	+																						+		
Hindlimb, rhabdomyosarcoma																							X		
Intercostal, fibroma	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+													
RESPIRATORY SYSTEM																									
Larynx	M	M	+	M		M	M	M	M	M	+	M													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal gland																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	M	+													
SPECIAL SENSES SYSTEM																									
Eye																									
Zymbal gland																						+			
Right, carcinoma																						X			
URINARY SYSTEM																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+		+	+	+		+	+	+			+	+	+
Urinary bladder	+	+	M	+	+	M	+	+	+	+	+	+													
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X			X					X	X	X	X	X	X	X	X			X		X	
Mesothelioma malignant																X									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	687	689	694	695	697	697	700	714	728	728	728	728	729	729	729	729	730	730	730	730	730	730	730	730	TOTAL TISSUES TUMORS
CARCASS ID	28511	26311	28811	25511	25711	26611	29211	27411	25611	26411	26811	26911	27211	25111	25211	26211	28411	27611	28011	28711	29411	29511	29711	29911	30101	
INTEGUMENTARY SYSTEM																									
Mammary gland				+			+	+		+		+	+	+	+					+				+		20
Adenocarcinoma																				X						1
Skin			+	+		+			+	+		+	+		+			+		+					23
Basosquamous tumor benign				X																						1
Keratoacanthoma						X														X						3
Keratoacanthoma, two													X													1
Subcutaneous tissue, fibroma			X																							1
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																									
Bone					+		+			+		+	+						+							18
Skeletal muscle																	+						+			4
Hindlimb, rhabdomyosarcoma																										1
Intercostal, fibroma																										1
NERVOUS SYSTEM																									
Brain										+		+	+													15
RESPIRATORY SYSTEM																									
Larynx										+		+	+													5
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																									X	1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea										+		+	+													14
SPECIAL SENSES SYSTEM																									
Eye						+	+																			2
Zymbal gland																										1
Right, carcinoma																										1
URINARY SYSTEM																									
Kidney			+		+	+	+	+	+	+		+	+					+		+	+	+		+		35
Urinary bladder										+			+													12
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X			X				X	X						X	X			X	X	X			26
Mesothelioma malignant																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 300 ppm

DAYS ON STUDY	506	512	519	529	541	541	548	548	567	575	589	611	617	638	644	647	648	653	660	666	667	669	678	679	694
CARCASS ID	19951	16611	15551	16651	17701	19021	15591	17711	16331	19411	18661	19611	17811	19881	15711	16991	18211	17911	18311	18111	19911	19111	16711	17611	15611
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, cecum	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, rectum	M	M	M	M	M	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	A	+
Jejunum, adenocarcinoma, mucinous	X																								
Intestine small, jejunum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mesentery									+	+			+											+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Pharynx																							+		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	M	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									
Pheochromocytoma benign						X								X						X					
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X		X									X		X	X	X	X	X	X		
Pars distalis, adenoma, multiple																									
Pars distalis, adenoma, two																									
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C cell, adenoma																									
C cell, adenoma													X			X								X	
C cell, carcinoma																						X			
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS		+																							
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	A	+
Adenoma																						X			
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Seminal vesicle	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X	X	X			X		X				X	X	X	X		X				X	X		X	
Interstitial cell, adenoma					X				X	X													X		

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 300 ppm (Continued)

DAYS ON STUDY	700	701	704	711	721	724	728	728	728	728	728	729	729	729	729	730	730	730	730	730	730	730	730	731	731	TOTAL
CARCASS ID	16021	15411	16011	15311	17511	18811	15211	15811	16811	17111	17211	15111	16111	16411	18411	17311	17411	18011	18511	18711	18911	19011	19311	19711	20011	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Jejunum, adenocarcinoma, mucinous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X																			1
Mesentery	+				+																					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth									+																	1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pheochromocytoma malignant		X										X														2
Pheochromocytoma complex						X																				1
Pheochromocytoma benign						X				X		X	X				X	X				X	X			11
Pheochromocytoma benign, multiple				X					X		X															3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X		X	X			X					X														5
Carcinoma							X																			1
Parathyroid gland	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X				X			X	X		X			X	X	X	X	X	X		28
Pars distalis, adenoma, multiple									X																	1
Pars distalis, adenoma, two							X																			1
Pars distalis, carcinoma																	X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C cell, adenoma											X															1
C cell, adenoma				X																			X	X		6
C cell, carcinoma																										1
Follicular cell, carcinoma																									X	1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma														X	X											2
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X			X	X		X	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	33
Interstitial cell, adenoma			X	X										X						X						8

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 300 ppm (Continued)

DAYS ON STUDY	506	512	519	529	541	541	548	548	567	575	589	611	617	638	644	647	648	653	660	666	667	669	678	679	694
CARCASS ID	19951	16611	15511	16511	17011	19211	15911	17711	16311	19411	18611	19611	17811	19811	15711	16911	18211	17911	18311	18111	19911	19111	16711	17611	15611
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Thymus	M	+	+	M	+	M	M	M	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	A	+
Thymoma malignant																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	M	M
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X										X				
Papilloma squamous																									
Trichoepithelioma													X												
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma					X																				
Subcutaneous tissue, neurofibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	M	M	M	M	M	M	+	+	M		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																	+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma												X													
Sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X			X		X	X	X		X	X	X	X		X								
Mesothelioma benign														X											

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 300 ppm (Continued)

DAYS ON STUDY	7 0 0	7 0 1	7 0 4	7 1 1	7 2 1	7 2 4	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	TOTAL TISSUES TUMORS
CARCASS ID	1 6 2 1	1 5 4 1	1 6 0 1	1 5 3 1	1 7 5 1	1 8 8 1	1 5 2 1	1 5 8 1	1 6 8 1	1 7 1 1	1 7 2 1	1 5 1 1	1 6 1 1	1 6 4 1	1 8 4 1	1 7 3 1	1 7 4 1	1 8 0 1	1 8 5 1	1 8 7 1	1 8 9 1	1 9 0 1	1 9 3 1	1 9 7 1	2 0 0 1	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	38
Thymoma malignant					X																				1
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Adenocarcinoma																						X			1
Fibroadenoma			X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																	X	X						X	5
Papilloma squamous																					X				1
Trichoepithelioma																									1
Subcutaneous tissue, fibroma																									1
Subcutaneous tissue, fibrosarcoma																									1
Subcutaneous tissue, neurofibroma																				X					1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																									
Eye	+	+	+																			+			5
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																	X								2
Sarcoma														X											1
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma															X									X	2
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X										X			X				X	X			X	20
Mesothelioma benign																									1

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

	Chamber Control	100 ppm	300 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	14/49 (29%)	(b) 6/21 (29%)	14/46 (30%)
Adjusted Rates (c)	51.1%		58.2%
Terminal Rates (d)	7/19 (37%)		9/18 (50%)
Day of First Observation	623		541
Life Table Test (e)			P=0.563N
Logistic Regression Test (e)			P=0.590N
Fisher Exact Test (e)			P=0.510
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	(b) 3/21 (14%)	2/46 (4%)
Adrenal Medulla: Complex Pheochromocytoma			
Overall Rates (a)	3/49 (6%)	(b) 0/21 (0%)	1/46 (2%)
Adjusted Rates (c)	12.0%		5.0%
Terminal Rates (d)	1/19 (5%)		0/18 (0%)
Day of First Observation	621		724
Life Table Test (e)			P=0.297N
Logistic Regression Test (e)			P=0.305N
Fisher Exact Test (e)			P=0.333N
Adrenal Medulla: Pheochromocytoma; Benign, Complex, or Malignant			
Overall Rates (a)	17/49 (35%)	(b) 8/21 (38%)	15/46 (33%)
Adjusted Rates (c)	60.4%		60.0%
Terminal Rates (d)	9/19 (47%)		9/18 (50%)
Day of First Observation	621		541
Life Table Test (e)			P=0.393N
Logistic Regression Test (e)			P=0.404N
Fisher Exact Test (e)			P=0.501N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/46 (4%)	(b) 2/18 (11%)	3/48 (6%)
Adjusted Rates (c)	7.6%		13.6%
Terminal Rates (d)	1/19 (5%)		2/19 (11%)
Day of First Observation	532		669
Life Table Test (e)			P=0.520
Logistic Regression Test (e)			P=0.530
Fisher Exact Test (e)			P=0.520
Pancreatic Islets: Adenoma			
Overall Rates (a)	6/46 (13%)	(b) 3/16 (19%)	5/49 (10%)
Adjusted Rates (c)	27.9%		21.6%
Terminal Rates (d)	4/19 (21%)		2/19 (11%)
Day of First Observation	697		700
Life Table Test (e)			P=0.470N
Logistic Regression Test (e)			P=0.445N
Fisher Exact Test (e)			P=0.455N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	31/49 (63%)	(b) 21/35 (60%)	30/50 (60%)
Adjusted Rates (c)	92.9%		80.0%
Terminal Rates (d)	17/19 (89%)		12/19 (63%)
Day of First Observation	506		512
Life Table Test (e)			P=0.395N
Logistic Regression Test (e)			P=0.375N
Fisher Exact Test (e)			P=0.449N

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

	Chamber Control	100 ppm	300 ppm
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	3/49 (6%)	(b) 1/35 (3%)	1/50 (2%)
Adjusted Rates (c)	11.9%		5.3%
Terminal Rates (d)	1/19 (5%)		1/19 (5%)
Day of First Observation	599		728
Life Table Test (e)			P=0.294N
Logistic Regression Test (e)			P=0.277N
Fisher Exact Test (e)			P=0.301N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	33/49 (67%)	(b) 22/35 (63%)	30/50 (60%)
Adjusted Rates (c)	93.4%		80.0%
Terminal Rates (d)	17/19 (89%)		12/19 (63%)
Day of First Observation	506		512
Life Table Test (e)			P=0.280N
Logistic Regression Test (e)			P=0.226N
Fisher Exact Test (e)			P=0.291N
Skin: Keratoacanthoma			
Overall Rates (f)	2/49 (4%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (c)	8.3%	17.7%	20.6%
Terminal Rates (d)	1/19 (5%)	2/17 (12%)	3/19 (16%)
Day of First Observation	638	479	589
Life Table Tests (e)	P=0.235	P=0.307	P=0.241
Logistic Regression Tests (e)	P=0.228	P=0.345	P=0.246
Cochran-Armitage Trend Test (e)	P=0.208		
Fisher Exact Test (e)		P=0.349	P=0.226
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (f)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (c)	13.6%	5.9%	2.2%
Terminal Rates (d)	2/19 (11%)	1/17 (6%)	0/19 (0%)
Day of First Observation	647	728	541
Life Table Tests (e)	P=0.251N	P=0.332N	P=0.279N
Logistic Regression Tests (e)	P=0.253N	P=0.308N	P=0.293N
Cochran-Armitage Trend Test (e)	P=0.266N		
Fisher Exact Test (e)		P=0.301N	P=0.301N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (f)	5/49 (10%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	20.8%	10.0%	5.2%
Terminal Rates (d)	3/19 (16%)	1/17 (6%)	0/19 (0%)
Day of First Observation	599	694	541
Life Table Tests (e)	P=0.181N	P=0.245N	P=0.191N
Logistic Regression Tests (e)	P=0.184N	P=0.212N	P=0.203N
Cochran-Armitage Trend Test (e)	P=0.198N		
Fisher Exact Test (e)		P=0.210N	P=0.210N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (f)	4/49 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	16.5%	8.0%	2.2%
Terminal Rates (d)	2/19 (11%)	1/17 (6%)	0/19 (0%)
Day of First Observation	643	519	541
Life Table Tests (e)	P=0.132N	P=0.359N	P=0.155N
Logistic Regression Tests (e)	P=0.148N	P=0.329N	P=0.172N
Cochran-Armitage Trend Test (e)	P=0.146N		
Fisher Exact Test (e)		P=0.329N	P=0.175N

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

	Chamber Control	100 ppm	300 ppm
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (f)	6/49 (12%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (c)	23.5%	12.0%	10.2%
Terminal Rates (d)	3/19 (16%)	1/17 (6%)	1/19 (5%)
Day of First Observation	599	519	541
Life Table Tests (e)	P=0.203N	P=0.270N	P=0.210N
Logistic Regression Tests (e)	P=0.?	P=0.233N	P=0.221N
Cochran-Armitage Trend Test (e)	P=0.226N		
Fisher Exact Test (e)		P=0.233N	P=0.233N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	35/49 (71%)	31/42 (74%)	41/50 (82%)
Adjusted Rates (c)	94.1%	93.2%	97.5%
Terminal Rates (d)	17/19 (89%)	14/16 (88%)	18/19 (95%)
Day of First Observation	422	484	506
Life Table Tests (e)	P=0.275	P=0.471N	P=0.332
Logistic Regression Tests (e)	P=0.206	P=0.516	P=0.220
Cochran-Armitage Trend Test (e)	P=0.131		
Fisher Exact Test (e)		P=0.494	P=0.157
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/49 (14%)	(b) 2/20 (10%)	7/50 (14%)
Adjusted Rates (c)	28.0%		26.8%
Terminal Rates (d)	2/19 (11%)		3/19 (16%)
Day of First Observation	647		617
Life Table Test (e)			P=0.566N
Logistic Regression Test (e)			P=0.548N
Fisher Exact Test (e)			P=0.597N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/49 (16%)	(b) 3/20 (15%)	8/50 (16%)
Adjusted Rates (c)	30.1%		29.3%
Terminal Rates (d)	2/19 (11%)		3/19 (16%)
Day of First Observation	623		617
Life Table Test (e)			P=0.552N
Logistic Regression Test (e)			P=0.541N
Fisher Exact Test (e)			P=0.590N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	25/49 (51%)	26/50 (52%)	20/50 (40%)
Adjusted Rates (c)	67.8%	67.2%	52.9%
Terminal Rates (d)	8/19 (42%)	7/17 (41%)	5/19 (26%)
Day of First Observation	422	393	512
Life Table Tests (e)	P=0.145N	P=0.462	P=0.190N
Logistic Regression Tests (e)	P=0.159N	P=0.542	P=0.196N
Cochran-Armitage Trend Test (e)	P=0.137N		
Fisher Exact Test (e)		P=0.541	P=0.184N
All Sites: Mesothelioma			
Overall Rates (f)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (c)	7.8%	2.9%	2.7%
Terminal Rates (d)	0/19 (0%)	0/17 (0%)	0/19 (0%)
Day of First Observation	492	623	638
Life Table Tests (e)	P=0.238N	P=0.301N	P=0.262N
Logistic Regression Tests (e)	P=0.334N	P=0.304N	P=0.402N
Cochran-Armitage Trend Test (e)	P=0.266N		
Fisher Exact Test (e)		P=0.301N	P=0.301N

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

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

TABLE A4a. HISTORICAL INCIDENCE OF KIDNEY MESENCHYMAL NEOPLASMS IN MALE F344/N RATS (a)

Study	Incidence of Lipomas in Controls
Historical Incidence for Chamber Controls in NTP Studies (b)	
Propylene oxide	0/50
Methyl methacrylate	0/50
Propylene	0/50
1,2-Epoxybutane	0/50
Dichloromethane	0/50
Tetrachloroethylene	0/49
Bromoethane	0/47
TOTAL	0/346
SD (c)	0.00%
Range (d)	
High	0/50
Low	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	2/1,590 (0.1%)
SD (c)	0.49%
Range (d)	
High	1/50
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Pacific Northwest Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL NEOPLASMS IN MALE F344/N RATS (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence for Chamber Controls in NTP Studies (b)	
Propylene oxide	(c) 1/48
Methyl methacrylate	0/49
Propylene	0/50
1,2-Epoxybutane	(d) 1/49
Dichloromethane	0/50
Tetrachloroethylene	(d) 1/46
Bromoethane	0/47
TOTAL	3/339 (0.9%)
SD (e)	1.12%
Range (f)	
High	1/46
Low	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies	
TOTAL	(d) 1/1,552 (0.1%)
SD (e)	0.37%
Range (f)	
High	1/48
Low	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Pacific Northwest Laboratories.
(c) Carcinoma
(d) Papilloma
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

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

	Chamber Control	100 ppm	300 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	24	29	28
Natural death	6	4	3
Survivors			
Terminal sacrifice	19	17	19
Wrong sex	1		
Animals examined microscopically	49	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(43)	(9)	(47)
Hyperplasia, lymphoid			1 (2%)
Parasite metazoan	2 (5%)		4 (9%)
Intestine large, colon	(46)	(13)	(49)
Hyperplasia, lymphoid			1 (2%)
Mineralization, multifocal			1 (2%)
Parasite metazoan	4 (9%)		6 (12%)
Artery, inflammation, chronic active, focal			1 (2%)
Intestine large, rectum	(36)	(12)	(40)
Parasite metazoan	2 (6%)		2 (5%)
Artery, submucosa, inflammation, chronic active, multifocal	1 (3%)		
Intestine small, duodenum	(45)	(14)	(48)
Inflammation, acute, multifocal		1 (7%)	
Inflammation, chronic, diffuse	1 (2%)		
Ulcer, two	1 (2%)		
Intestine small, ileum	(44)	(12)	(44)
Inflammation, chronic active, multifocal			1 (2%)
Liver	(49)	(42)	(50)
Angiectasis, focal	3 (6%)	3 (7%)	2 (4%)
Angiectasis, multifocal	3 (6%)		3 (6%)
Basophilic focus	1 (2%)	4 (10%)	3 (6%)
Basophilic focus, multiple	1 (2%)	3 (7%)	1 (2%)
Congestion		2 (5%)	
Cytomegaly, focal		1 (2%)	
Cytomegaly, multifocal		1 (2%)	
Cytoplasmic alteration, focal	2 (4%)		1 (2%)
Degeneration, ballooning, focal	3 (6%)		3 (6%)
Eosinophilic focus	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus, multiple	1 (2%)		
Fatty change, diffuse	1 (2%)	3 (7%)	1 (2%)
Fatty change, focal	2 (4%)	1 (2%)	
Fatty change, multifocal	1 (2%)	3 (7%)	8 (16%)
Granuloma, multifocal	4 (8%)		4 (8%)
Hematopoietic cell proliferation, multifocal	1 (2%)		
Hemorrhage, multifocal	2 (4%)		1 (2%)
Hepatodiaphragmatic nodule	3 (6%)	3 (7%)	3 (6%)
Hepatodiaphragmatic nodule, multiple		1 (2%)	
Hyperplasia, nodular, focal			1 (2%)
Hyperplasia, nodular, multifocal	1 (2%)		
Mitotic alteration		2 (5%)	
Necrosis, focal		1 (2%)	1 (2%)
Necrosis, multifocal	12 (24%)	3 (7%)	8 (16%)
Pigmentation, multifocal		1 (2%)	
Thrombus, two	1 (2%)		
Vacuolization cytoplasmic, multifocal		1 (2%)	
Bile duct, fibrosis, multifocal	2 (4%)		1 (2%)
Bile duct, hyperplasia, multifocal	32 (65%)	23 (55%)	30 (60%)

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

	Chamber Control	100 ppm	300 ppm
ALIMENTARY SYSTEM			
Liver (Continued)	(49)	(42)	(50)
Centrilobular, congestion, diffuse	1 (2%)		
Centrilobular, degeneration, diffuse	2 (4%)	5 (12%)	1 (2%)
Centrilobular, degeneration, multifocal			4 (8%)
Centrilobular, fatty change, diffuse	11 (22%)	2 (5%)	4 (8%)
Centrilobular, fatty change, multifocal	1 (2%)		
Centrilobular, necrosis, diffuse	5 (10%)		
Centrilobular, necrosis, multifocal	1 (2%)	1 (2%)	
Periportal, cytomegaly, diffuse			1 (2%)
Periportal, fatty change, diffuse	1 (2%)	1 (2%)	2 (4%)
Portal, fibrosis, multifocal		1 (2%)	
Portal, inflammation, chronic, multifocal	1 (2%)		
Portal, inflammation, chronic active, multifocal	2 (4%)	1 (2%)	
Mesentery	(8)	(4)	(6)
Accessory spleen, two			1 (17%)
Hemorrhage, acute, multifocal	1 (13%)		
Inflammation, chronic active, multifocal			1 (17%)
Artery, ectasia, multifocal		1 (25%)	
Artery, inflammation, chronic, focal			1 (17%)
Artery, inflammation, chronic, multifocal	1 (13%)	1 (25%)	
Artery, mineralization, multifocal		1 (25%)	1 (17%)
Fat, necrosis, focal		1 (25%)	
Pancreas	(46)	(19)	(49)
Infiltration cellular, lymphocytic, focal	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	2 (4%)		
Acinus, atrophy, diffuse	3 (7%)	1 (5%)	
Acinus, atrophy, focal	5 (11%)		2 (4%)
Acinus, atrophy, multifocal	18 (39%)	2 (11%)	20 (41%)
Acinus, hyperplasia, focal			1 (2%)
Acinus, hyperplasia, multifocal	1 (2%)		
Artery, ectasia, multifocal		1 (5%)	
Artery, fibrosis		1 (5%)	
Artery, inflammation, chronic, multifocal		1 (5%)	
Artery, inflammation, chronic active, focal			2 (4%)
Artery, inflammation, chronic active, multifocal	2 (4%)		1 (2%)
Artery, mineralization, multifocal		1 (5%)	
Pharynx	(1)	(1)	(1)
Inflammation, chronic active, multifocal		1 (100%)	
Palate, inflammation, chronic, focal	1 (100%)		1 (100%)
Salivary glands	(48)	(18)	(50)
Artery, inflammation, chronic active, multifocal	1 (2%)		
Stomach, forestomach	(48)	(13)	(49)
Inflammation, chronic active	5 (10%)	2 (15%)	5 (10%)
Mineralization, diffuse			1 (2%)
Ulcer	3 (6%)	1 (8%)	3 (6%)
Epithelium, hyperplasia	6 (13%)	2 (15%)	6 (12%)
Submucosa, edema, diffuse			1 (2%)
Submucosa, inflammation, subacute	1 (2%)		
Stomach, glandular	(47)	(14)	(50)
Cyst, multiple	1 (2%)		
Infiltration cellular, lymphocytic		1 (7%)	
Inflammation, chronic active, focal			1 (2%)
Mineralization, diffuse			1 (2%)
Mineralization, multifocal	1 (2%)		
Ulcer, acute	2 (4%)		
Tooth	(2)	(3)	(1)
Dysplasia		3 (100%)	
Pulp, angiectasis	1 (50%)		

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

	Chamber Control	100 ppm	300 ppm
CARDIOVASCULAR SYSTEM			
Heart	(49)	(14)	(50)
Cardiomyopathy	42 (86%)	10 (71%)	40 (80%)
Mineralization, multifocal			1 (2%)
Atrium left, thrombus	4 (8%)	1 (7%)	2 (4%)
Endocardium, atrium, fibrosis, focal	1 (2%)		
Myocardium, fibrosis, focal			1 (2%)
Valve, fibrosis, focal	1 (2%)		1 (2%)
Valve, inflammation, proliferative, focal			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(24)	(50)
Capsule, accessory adrenal cortical nodule	5 (10%)	2 (8%)	4 (8%)
Adrenal gland, cortex	(49)	(20)	(50)
Cytoplasmic alteration, focal	1 (2%)		1 (2%)
Degeneration, fatty, diffuse	13 (27%)	5 (25%)	9 (18%)
Degeneration, fatty, focal	6 (12%)	4 (20%)	6 (12%)
Degeneration, fatty, multifocal	3 (6%)	1 (5%)	3 (6%)
Hyperplasia, focal	4 (8%)	2 (10%)	10 (20%)
Hyperplasia, multifocal	3 (6%)		2 (4%)
Hypertrophy, focal		2 (10%)	1 (2%)
Hypertrophy, multifocal			1 (2%)
Adrenal gland, medulla	(49)	(21)	(46)
Angiectasis, focal	1 (2%)		
Hyperplasia, focal	8 (16%)	3 (14%)	5 (11%)
Hyperplasia, multifocal	10 (20%)	2 (10%)	4 (9%)
Islets, pancreatic	(46)	(16)	(49)
Atrophy, diffuse	1 (2%)		
Hyperplasia	1 (2%)		
Hyperplasia, focal	2 (4%)		2 (4%)
Hyperplasia, multifocal	1 (2%)	2 (13%)	5 (10%)
Inflammation, multifocal			1 (2%)
Parathyroid gland	(45)	(14)	(45)
Hyperplasia	1 (2%)	2 (14%)	5 (11%)
Pituitary gland	(49)	(35)	(50)
Pars distalis, angiectasis	2 (4%)	1 (3%)	3 (6%)
Pars distalis, cyst	1 (2%)	4 (11%)	5 (10%)
Pars distalis, degeneration, fatty, focal			1 (2%)
Pars distalis, hyperplasia		1 (3%)	2 (4%)
Pars distalis, hyperplasia, eosinophil, diffuse	1 (2%)		
Pars distalis, hyperplasia, focal	2 (4%)	3 (9%)	7 (14%)
Pars distalis, hyperplasia, multifocal	5 (10%)		
Pars distalis, pigmentation, focal	1 (2%)		
Pars intermedia, hyperplasia	2 (4%)		
Thyroid gland	(49)	(20)	(50)
Cyst	1 (2%)		
Mineralization, multifocal	1 (2%)		
C-cell, hyperplasia, focal	4 (8%)	1 (5%)	2 (4%)
C-cell, hyperplasia, multifocal	4 (8%)	1 (5%)	3 (6%)
Follicle, cyst			2 (4%)
Follicular cell, degeneration, multifocal	1 (2%)		1 (2%)
Follicular cell, hyperplasia, focal	1 (2%)		
GENERAL BODY SYSTEM			
Tissue, NOS	(1)		(1)
Necrosis, focal			1 (100%)

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

	Chamber Control	100 ppm	300 ppm
GENITAL SYSTEM			
Epididymis	(47)	(16)	(50)
Dilatation, multifocal	2 (4%)		1 (2%)
Granuloma sperm, single	1 (2%)		1 (2%)
Inflammation, suppurative, focal	1 (2%)		
Left, atrophy			1 (2%)
Preputial gland	(46)	(18)	(48)
Abscess		2 (11%)	
Atrophy, diffuse	1 (2%)		
Ectasia	2 (4%)	2 (11%)	3 (6%)
Fibrosis, diffuse	2 (4%)		
Inflammation, chronic active	4 (9%)		4 (8%)
Inflammation, granulomatous, diffuse	1 (2%)		1 (2%)
Inflammation, granulomatous, focal	4 (9%)		3 (6%)
Inflammation, granulomatous, multifocal	18 (39%)	4 (22%)	22 (46%)
Inflammation, suppurative, focal	1 (2%)		
Prostate	(49)	(18)	(49)
Hyperplasia, focal	5 (10%)		5 (10%)
Hyperplasia, multifocal	3 (6%)	2 (11%)	6 (12%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic active	8 (16%)	6 (33%)	13 (27%)
Seminal vesicle	(41)	(13)	(43)
Atrophy, diffuse	3 (7%)		5 (12%)
Fibrosis, multifocal			1 (2%)
Inflammation, subacute, diffuse	1 (2%)		
Inflammation, suppurative, chronic active, diffuse			1 (2%)
Testes	(49)	(42)	(50)
Hemorrhage		1 (2%)	
Mineralization, focal	1 (2%)		
Mineralization, multifocal	1 (2%)	1 (2%)	1 (2%)
Arteriole, inflammation	6 (12%)	2 (5%)	4 (8%)
Capsule, hyperplasia, multifocal			1 (2%)
Interstitial cell, hyperplasia	2 (4%)	4 (10%)	2 (4%)
Seminiferous tubule, atrophy	13 (27%)	11 (26%)	13 (26%)
Seminiferous tubule, degeneration	2 (4%)		4 (8%)
Serosa, necrosis, focal	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(48)	(15)	(50)
Atrophy		1 (7%)	
Hyperplasia	8 (17%)	2 (13%)	5 (10%)
Metaplasia, osseous	1 (2%)	1 (7%)	
Myelofibrosis	1 (2%)		
Myeloid cell, hyperplasia	4 (8%)		4 (8%)
Lymph node	(49)	(27)	(50)
Inflammation, suppurative, focal	1 (2%)		
Lumbar, hemorrhage			1 (2%)
Lumbar, inflammation, granulomatous, multifocal	1 (2%)		
Mediastinal, hemorrhage	2 (4%)	2 (7%)	5 (10%)
Mediastinal, hyperplasia, lymphoid	1 (2%)		
Mediastinal, hyperplasia, re cell	1 (2%)		
Mediastinal, pigmentation, hemosiderin	2 (4%)		
Pancreatic, hemorrhage		1 (4%)	
Pancreatic, hyperplasia, lymphoid	2 (4%)		
Lymph node, mandibular	(44)	(14)	(48)
Hemorrhage		1 (7%)	1 (2%)
Hyperplasia, lymphoid	2 (5%)		3 (6%)
Hyperplasia, plasma cell	2 (5%)	1 (7%)	5 (10%)
Hyperplasia, re cell	1 (2%)		
Inflammation, subacute, focal	1 (2%)		

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

	Chamber Control	100 ppm	300 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mesenteric	(44)	(17)	(48)
Depletion lymphoid	1 (2%)		1 (2%)
Fibrosis, multifocal			1 (2%)
Hemorrhage		2 (12%)	2 (4%)
Hyperplasia, lymphoid	2 (5%)		2 (4%)
Hyperplasia, re cell	1 (2%)		3 (6%)
Spleen	(49)	(35)	(49)
Congestion		1 (3%)	1 (2%)
Depletion lymphoid			1 (2%)
Fibrosis, focal	1 (2%)	2 (6%)	4 (8%)
Fibrosis, multifocal	2 (4%)	2 (6%)	
Hematopoietic cell proliferation	4 (8%)	2 (6%)	
Necrosis, coagulative, focal	1 (2%)		
Pigmentation, hemosiderin	3 (6%)	1 (3%)	7 (14%)
Thrombus, single			1 (2%)
Capsule, fibrosis, focal			1 (2%)
Capsule, fibrosis, multifocal	1 (2%)		1 (2%)
Thymus	(38)	(14)	(38)
Angiectasis, multifocal		1 (7%)	
Depletion lymphoid			1 (3%)
Hemorrhage	1 (3%)	1 (7%)	
Hyperplasia, tubular	8 (21%)	2 (14%)	6 (16%)
Artery, inflammation, chronic active	1 (3%)		1 (3%)
INTEGUMENTARY SYSTEM			
Mammary gland	(38)	(20)	(46)
Ectasia, diffuse	9 (24%)	4 (20%)	4 (9%)
Ectasia, multifocal	14 (37%)	7 (35%)	6 (13%)
Granuloma			1 (2%)
Hyperplasia, diffuse	3 (8%)	2 (10%)	7 (15%)
Hyperplasia, focal			1 (2%)
Inflammation, chronic active, multifocal	2 (5%)		
Inflammation, granulomatous		1 (5%)	
Inflammation, proliferative	2 (5%)		
Skin	(49)	(23)	(50)
Cyst epithelial inclusion	1 (2%)	3 (13%)	
Hyperkeratosis	1 (2%)	2 (9%)	
Hyperplasia, squamous	1 (2%)	1 (4%)	
Inflammation, chronic, focal	1 (2%)		1 (2%)
Ulcer			1 (2%)
Artery, subcutaneous tissue, inflammation, chronic active, focal	1 (2%)		
Subcutaneous tissue, cyst			1 (2%)
Subcutaneous tissue, hemorrhage, chronic, focal	1 (2%)		
Subcutaneous tissue, inflammation, chronic active		2 (9%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(18)	(50)
Fibrous osteodystrophy		3 (17%)	2 (4%)
Osteopetrosis			1 (2%)
Sternum, developmental malformation	1 (2%)		
Skeletal muscle	(2)	(4)	(1)
Hemorrhage, acute		2 (50%)	

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

	Chamber Control	100 ppm	300 ppm
NERVOUS SYSTEM			
Brain	(49)	(15)	(50)
Compression	11 (22%)	5 (33%)	9 (18%)
Hemorrhage, focal	4 (8%)		1 (2%)
Hemorrhage, multifocal	1 (2%)		2 (4%)
Hydrocephalus	3 (6%)	2 (13%)	8 (16%)
Perivascular, infiltration cellular, mixed cell, multifocal		1 (7%)	
Thalamus, gliosis, focal	1 (2%)		
RESPIRATORY SYSTEM			
Larynx	(37)	(5)	(41)
Inflammation, chronic, multifocal			2 (5%)
Inflammation, chronic active, focal	7 (19%)	1 (20%)	5 (12%)
Inflammation, suppurative, focal	1 (3%)		
Submucosa, dilatation			1 (2%)
Lung	(49)	(50)	(50)
Edema, focal	1 (2%)		
Hemorrhage, subacute, multifocal	1 (2%)		1 (2%)
Mineralization, multifocal			1 (2%)
Alveolar epithelium, hyperplasia, focal		1 (2%)	
Alveolar epithelium, hyperplasia, multifocal		2 (4%)	
Artery, mineralization, focal			1 (2%)
Bronchus, hyperplasia, lymphoid, focal			1 (2%)
Bronchus, epithelium, hyperplasia, focal	1 (2%)		
Interstitium, inflammation, acute, multifocal			1 (2%)
Interstitium, inflammation, chronic, diffuse		1 (2%)	
Interstitium, inflammation, chronic, focal	1 (2%)		
Interstitium, inflammation, chronic, multifocal	2 (4%)	4 (8%)	2 (4%)
Interstitium, inflammation, chronic active, multifocal			2 (4%)
Interstitium, mineralization, multifocal		1 (2%)	
Vein, mineralization, multifocal	1 (2%)		
Nose	(48)	(50)	(50)
Lumen, exudate	2 (4%)	5 (10%)	2 (4%)
Lumen, foreign body	2 (4%)	5 (10%)	4 (8%)
Mucosa, inflammation, chronic	4 (8%)	4 (8%)	6 (12%)
Mucosa, inflammation, chronic active	2 (4%)	9 (18%)	4 (8%)
Mucosa, thrombus, multifocal	5 (10%)	5 (10%)	3 (6%)
Nasolacrimal duct, exudate	1 (2%)	3 (6%)	3 (6%)
Nasolacrimal duct, fungus			1 (2%)
Nasolacrimal duct, hyperplasia	1 (2%)		
Nasolacrimal duct, inflammation, acute		1 (2%)	
Nasolacrimal duct, inflammation, chronic	14 (29%)	16 (32%)	10 (20%)
Nasolacrimal duct, inflammation, chronic active	5 (10%)	1 (2%)	5 (10%)
Olfactory epithelium, atrophy	2 (4%)	1 (2%)	3 (6%)
Olfactory epithelium, cyst		4 (8%)	6 (12%)
Olfactory epithelium, erosion		8 (16%)	1 (2%)
Olfactory epithelium, hyperplasia, eosinophil	1 (2%)		
Olfactory epithelium, inflammation, chronic active			1 (2%)
Olfactory epithelium, metaplasia		6 (12%)	4 (8%)
Respiratory epithelium, cyst	2 (4%)	13 (26%)	9 (18%)
Respiratory epithelium, hyperplasia	8 (17%)	24 (48%)	27 (54%)
Respiratory epithelium, hyperplasia, eosinophil	4 (8%)		1 (2%)
Respiratory epithelium, hyperplasia, papillary		5 (10%)	2 (4%)
Trachea	(48)	(14)	(50)
Inflammation, chronic		1 (7%)	2 (4%)
Artery, inflammation, chronic active, focal	1 (2%)		
Glands, metaplasia, squamous, focal			1 (2%)

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

	Chamber Control	100 ppm	300 ppm
SPECIAL SENSES SYSTEM			
Eye	(3)	(2)	(5)
Anterior, synechia		1 (50%)	
Cornea, inflammation, chronic active		1 (50%)	
Left, choroid, hemorrhage	1 (33%)		
Retina, degeneration	1 (33%)	1 (50%)	
Right, lens, cataract		1 (50%)	
URINARY SYSTEM			
Kidney	(49)	(35)	(50)
Bacterium		1 (3%)	
Infiltration cellular, lymphocytic, multifocal		1 (3%)	
Inflammation, suppurative, acute, multifocal		1 (3%)	
Inflammation, suppurative, focal			1 (2%)
Mineralization, diffuse			1 (2%)
Nephropathy, chronic	46 (94%)	32 (91%)	48 (96%)
Pigmentation, diffuse	8 (16%)	2 (6%)	5 (10%)
Pigmentation, multifocal	2 (4%)	1 (3%)	1 (2%)
Artery, inflammation, chronic active, focal			1 (2%)
Cortex, cyst	1 (2%)	1 (3%)	3 (6%)
Cortex, hyperplasia, atypical	1 (2%)		2 (4%)
Proximal convoluted renal tubule, necrosis, acute, multifocal			1 (2%)
Transitional epithelium, hyperplasia	2 (4%)		
Transitional epithelium, mineralization	4 (8%)		
Urinary bladder	(48)	(12)	(49)
Calculus gross observation	1 (2%)		
Ectasia			1 (2%)
Inflammation, chronic active, focal	1 (2%)		
Inflammation, subacute, diffuse			1 (2%)
Lumen, calculus micro observation only, single	1 (2%)		
Subserosa, mineralization, focal			1 (2%)

APPENDIX B

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

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

	Chamber Control	100 ppm	300 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	16	21	18
Natural death	3	1	6
Survivors			
Terminal sacrifice	31	28	26
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(5)	(46)
Intestine large, colon	(50)	(10)	(49)
Intestine large, rectum	(46)	(9)	(46)
Intestine small, duodenum	(50)	(9)	(50)
Intestine small, ileum	(48)	(7)	(48)
Intestine small, jejunum	(48)	(7)	(49)
Liver	(50)	(33)	(50)
Mesentery	(4)	(2)	(5)
Fibrosarcoma, metastatic, skin		1 (50%)	
Fat, lipoma	1 (25%)		
Pancreas	(50)	(13)	(49)
Carcinoma	1 (2%)		
Salivary glands	(50)	(9)	(47)
Stomach, forestomach	(49)	(11)	(49)
Stomach, glandular	(50)	(11)	(50)
Tongue			(1)
Squamous cell carcinoma			1 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(10)	(50)
Hemangiosarcoma, metastatic, uncertain primary site			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(14)	(50)
Adrenal gland, cortex	(50)	(14)	(50)
Adenoma	1 (2%)		
Adrenal gland, medulla	(48)	(14)	(45)
Pheochromocytoma malignant	2 (4%)		1 (2%)
Pheochromocytoma benign	5 (10%)		3 (7%)
Islets, pancreatic	(50)	(12)	(49)
Adenoma	1 (2%)		1 (2%)
Carcinoma	1 (2%)	1 (8%)	2 (4%)
Pituitary gland	(50)	(43)	(50)
Pars distalis, adenoma	25 (50%)	24 (56%)	24 (48%)
Pars distalis, adenoma, multiple		1 (2%)	1 (2%)
Pars distalis, adenoma, two	3 (6%)	1 (2%)	4 (8%)
Pars distalis, carcinoma	4 (8%)	2 (5%)	1 (2%)
Thyroid gland	(50)	(10)	(50)
Carcinoma			1 (2%)
C-cell, adenoma	7 (14%)		2 (4%)
C-cell, carcinoma			2 (4%)
Follicular cell, adenoma, papillary			1 (2%)
Follicular cell, carcinoma			1 (2%)
GENERAL BODY SYSTEM			
None			

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

	Chamber Control	100 ppm	300 ppm
GENITAL SYSTEM			
Clitoral gland	(48)	(11)	(46)
Adenoma	1 (2%)	2 (18%)	2 (4%)
Carcinoma		2 (18%)	
Duct, papilloma squamous	1 (2%)		
Ovary	(50)	(18)	(50)
Uterus	(50)	(18)	(50)
Adenoma	1 (2%)		
Leiomyoma		1 (6%)	1 (2%)
Leiomyosarcoma	1 (2%)	1 (6%)	
Polyp stromal	7 (14%)	6 (33%)	5 (10%)
Sarcoma stromal	1 (2%)		
Vagina	(1)		(1)
Schwannoma malignant			1 (100%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(9)	(50)
Lymph node	(50)	(17)	(50)
Lymph node, mandibular	(47)	(11)	(47)
Lymph node, mesenteric	(47)	(12)	(46)
Spleen	(50)	(19)	(50)
Thymus	(38)	(6)	(37)
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(29)	(49)
Adenocarcinoma	3 (6%)		2 (4%)
Adenoma		1 (3%)	1 (2%)
Carcinoma		1 (3%)	
Fibroadenoma	13 (27%)	8 (28%)	9 (18%)
Fibroadenoma, multiple	1 (2%)		
Fibroadenoma, two	2 (4%)		
Skin	(50)	(13)	(50)
Basal cell carcinoma			1 (2%)
Papilloma squamous	1 (2%)		
Squamous cell carcinoma	1 (2%)		
Subcutaneous tissue, fibroma	3 (6%)	2 (15%)	1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (8%)	1 (2%)
Subcutaneous tissue, lipoma			1 (2%)
Subcutaneous tissue, myxoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(9)	(50)
Sternum, osteosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(11)	(50)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland			1 (2%)
Trachea	(50)	(8)	(50)
SPECIAL SENSES SYSTEM			
None			

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

	Chamber Control	100 ppm	300 ppm
URINARY SYSTEM			
Kidney	(50)	(14)	(50)
Urinary bladder	(49)	(9)	(46)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	20 (40%)	16 (32%)	25 (50%)
TUMOR SUMMARY			
Total animals with primary neoplasms **	48	41	46
Total primary neoplasms	108	70	97
Total animals with benign neoplasms	44	34	39
Total benign neoplasms	73	46	57
Total animals with malignant neoplasms	28	23	31
Total malignant neoplasms	35	24	40
Total animals with secondary neoplasms ***		1	2
Total secondary neoplasms		1	2
Total animals with malignant neoplasms--uncertain primary site			1

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

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

DAYS ON STUDY	1 6 6	4 3 4	4 7 0	5 4 5	5 5 3	5 8 2	5 9 2	5 9 2	6 1 3	6 3 0	6 3 0	6 3 5	6 5 9	6 7 9	6 8 8	7 0 1	7 0 8	7 0 8	7 1 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9
CARCASS ID	1 8 1	2 8 1	3 5 1	1 3 1	3 1 1	1 5 1	1 1 1	3 6 1	0 5 1	2 3 1	3 3 1	4 6 1	5 0 1	0 2 1	2 2 1	0 8 1	3 7 1	4 7 1	2 5 1	0 7 1	1 9 1	2 0 1	2 1 1	0 3 1	0 4 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																		+					+	+	
Fat, lipoma																								X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pheochromocytoma malignant				X														X							
Pheochromocytoma benign								X								X					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X				X	X		X		X			X	X		X		
Pars distalis, adenoma, two									X																
Pars distalis, carcinoma								X															X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma								X					X	X										X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma															X										
Duct, papilloma squamous																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Leiomyosarcoma																									
Polyp stromal		X												X	X										
Sarcoma stromal																									
Vagina											+														

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

DAYS ON STUDY	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	TOTAL
CARCASS ID	0061	0091	1011	1211	1611	1711	2411	4911	0111	1411	3411	4441	4551	4881	2611	2771	2991	3011	3211	3881	3991	4001	4111	4211	4311	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																									+	4
Fat, lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																										2
Pheochromocytoma benign								X											X							5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Carcinoma															X											1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X			X		X	X	X	X	X	X				X		X	X		X	25
Pars distalis, adenoma, two																					X			X		3
Pars distalis, carcinoma	X									X																4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X							X									X					7
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Duct, papilloma squamous													X													1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leiomyosarcoma																	X									1
Polyp stromal	X												X		X	X										7
Sarcoma stromal							X																			1
Vagina																										1

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

DAYS ON STUDY	1 6 6	4 3 4	4 7 0	5 4 5	5 5 3	5 8 2	5 9 2	5 9 2	6 1 3	6 3 0	6 3 0	6 3 5	6 5 9	6 7 9	6 8 8	7 0 1	7 0 8	7 0 8	7 1 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9
CARCASS ID	1 8 1	2 8 1	3 5 1	1 3 1	3 1 1	1 5 1	1 1 1	3 6 1	0 5 1	2 3 1	3 3 1	4 6 1	5 0 1	0 2 1	2 2 1	0 8 1	3 7 1	4 7 1	2 5 1	0 7 1	1 9 1	2 0 1	2 1 1	0 3 1	0 4 1
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X															X		
Fibroadenoma							X	X		X								X	X	X		X			
Fibroadenoma, multiple																									
Fibroadenoma, two											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Squamous cell carcinoma															X										
Subcutaneous tissue, fibroma		X			X														X						
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye												+		+											
Zymbal gland															+										
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X	X	X	X	X		X	X	X	X			X	X	X	X	X

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

DAYS ON STUDY	729	729	729	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	TOTAL
CARCASS ID	061	091	101	121	161	171	241	491	011	141	341	441	451	481	261	271	291	301	321	381	391	401	411	421	431	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood				+																						1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	M	M	M	+	+	+	+	M	+	38
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																						X				3
Fibroadenoma		X					X	X							X	X									X	13
Fibroadenoma, multiple																		X								1
Fibroadenoma, two			X																							2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																							X			1
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, fibrosarcoma																		X								1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										2
Zymbal gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X					X								X		X			20

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 100 ppm

DAYS ON STUDY	4 2 1	4 9 5	4 9 9	5 2 6	5 4 8	5 6 0	5 8 3	6 2 4	6 2 4	6 3 7	6 3 7	6 5 9	6 6 1	6 7 5	6 9 3	6 9 6	7 0 1	7 0 3	7 0 7	7 0 7	7 0 9	7 1 4	7 2 8	7 2 8	7 2 8
CARCASS ID	2 2 3 1	2 0 7 1	2 1 0 1	2 4 4 1	2 0 6 1	2 4 2 1	2 4 6 1	2 2 6 1	2 3 1 1	2 4 7 1	2 4 8 1	2 1 1 1	2 2 8 1	2 3 7 1	2 1 4 1	2 2 0 1	2 0 2 1	2 1 9 1	2 3 2 1	2 4 1 1	2 3 5 1	2 1 2 1	2 3 3 1	2 3 4 1	2 3 6 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+																
Intestine large	+	+	+	+	+	+	+	+	+	+															
Intestine large, cecum	M	M	+	M	+	+		+	+																
Intestine large, colon	+	+	+	+	+	+	+	+	+	+															
Intestine large, rectum	+	+	+	+	+	+	+	+	+																
Intestine small	+	+	+	+	+	+	+	+	+																
Intestine small, duodenum	+	+	+	+	+	+	+	+	+																
Intestine small, ileum	+	A	+	+	+	+	+	M	+																
Intestine small, jejunum	+	A	+	M	+	+	+	+	+																
Liver	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+			
Mesentery										+							+								
Fibrosarcoma, metastatic, skin																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+															
Salivary glands	+	+	+	+	+	+	+	+	+																
Stomach	+	+	+	+	+	+	+	+	+																
Stomach, forestomach	+	+	+	+	+	+	+	+	+																
Stomach, glandular	+	+	+	+	+	+	+	+	+																
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+																
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+				+												
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+				+												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+				+												
Islets, pancreatic	+	+	+	+	+	+	+	+	+																
Carcinoma																									
Parathyroid gland	M	M	+	+	+	+	+	+	+																
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	
Pars distalis, adenoma		X				X			X	X	X		X			X	X	X	X						
Pars distalis, adenoma, multiple																				X					
Pars distalis, adenoma, two														X											
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+						+										
GENERAL BODY SYSTEM																									
Tissue, NOS							+																		
GENITAL SYSTEM																									
Clitoral gland	+	M	+	+	M	M	M	+	+				+				+								
Adenoma													X												
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+				+							+		+		+	
Uterus	+	+	+	+	+	+	+	+	+												+			+	+
Leiomyoma																									
Leiomyosarcoma																									X
Polyp stromal				X																				X	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+																
Lymph node	+	+	+	+	+	+	+	+	+	+				+		+	+	+							
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+				+											
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+							+	+								
Spleen	+	+	+	+	+	+	+	+	+	+		+		+				+	+		+	+			
Thymus	M	+	+	+	+	M	+	+	M																
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+				+	+	+		+	+	+	+				+	+
Adenoma																									
Carcinoma						X																			
Fibroadenoma							X												X						X
Skin	+	+	+	+	+	+	+	+	+		+						+								
Subcutaneous tissue, fibroma											X														
Subcutaneous tissue, fibrosarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+			+													
RESPIRATORY SYSTEM																									
Larynx	M	+	+		+	+	M	+	+																
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	M	+	+	+	+	+	+	+																
SPECIAL SENSES SYSTEM																									
Eye								+				+					+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+				+		+				+						
Urinary bladder	+	+	+	+	+	+	M	+	+				+												
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X				X	X	X		X		X				X	X		X	X			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 ppm (Continued)

DAYS ON STUDY	728	728	728	729	729	729	729	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	TOTAL TISSUES TUMORS
CARCASS ID	24501	24901	25001	22901	23001	24001	24301	22101	22201	22401	22501	22701	23801	23901	20101	20301	20401	20501	20801	20901	21301	21501	21601	21701	21801	
ALIMENTARY SYSTEM																										
Esophagus																										9
Intestine large																										10
Intestine large, cecum																										5
Intestine large, colon																										10
Intestine large, rectum																										9
Intestine small																										9
Intestine small, duodenum																										9
Intestine small, ileum																										7
Intestine small, jejunum																										7
Liver	+				+	+	+			+		+			+		+	+	+	+		+		+		33
Mesentery																										2
Fibrosarcoma, metastatic, skin																										1
Pancreas	+										+											+				13
Salivary glands																										9
Stomach	+		+																							11
Stomach, forestomach	+		+																							11
Stomach, glandular	+		+																							11
CARDIOVASCULAR SYSTEM																										
Heart																	+									10
ENDOCRINE SYSTEM																										
Adrenal gland							+				+				+		+									14
Adrenal gland, cortex							+				+				+		+									14
Adrenal gland, medulla							+				+				+		+									14
Islets, pancreatic	+										+											+				12
Carcinoma	X																									1
Parathyroid gland																										7
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	+	+		+			+	43
Pars distalis, adenoma	X	X	X	X	X		X	X	X						X	X	X	X	X			X				24
Pars distalis, adenoma, multiple																										1
Pars distalis, adenoma, two																										1
Pars distalis, carcinoma						X																			X	2
Thyroid gland																										10
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Clitoral gland						+									+		+			+						11
Adenoma						X																				2
Carcinoma															X					X						2
Ovary							+										+	+	+		+					18
Uterus	+							+	+				+					+					+			18
Leiomyoma																							X			1
Leiomyosarcoma																										1
Polyp stromal								X	X				X					X								6
HEMATOPOIETIC SYSTEM																										
Bone marrow																										9
Lymph node	+							+							+											17
Lymph node, mandibular															+											11
Lymph node, mesenteric								+							+											12
Spleen	+						+															+				19
Thymus																										6
INTEGUMENTARY SYSTEM																										
Mammary gland	+		+	+		+	+	+				+			+		+	+	+	+						29
Adenoma	X																									1
Carcinoma																										1
Fibroadenoma			X	X				X							X					X						8
Skin			+																			+				13
Subcutaneous tissue, fibroma																						X				2
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										9
NERVOUS SYSTEM																										
Brain						+																				11
RESPIRATORY SYSTEM																										
Larynx																										6
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	–	+	+	49
Trachea																										8
SPECIAL SENSES SYSTEM																										
Eye																										3
URINARY SYSTEM																										
Kidney	+														+											14
Urinary bladder																										9
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X						X															X				16

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 300 ppm

DAYS ON STUDY	4 1 4	4 3 4	4 4 4	4 5 6	4 9 9	5 0 6	5 2 6	5 7 6	5 7 6	5 8 2	6 0 6	6 1 4	6 2 6	6 3 7	6 4 6	6 8 0	6 8 1	6 8 3	6 9 0	6 9 7	7 0 9	7 0 9	7 1 4	7 1 8	7 2 8
CARCASS ID	1 0 5 1	1 3 1 1	1 0 4 1	1 1 1 1	1 1 6 1	1 4 9 1	1 4 7 1	1 3 4 1	1 3 6 1	1 4 4 1	1 1 2 1	1 3 2 1	1 4 2 1	1 3 7 1	1 2 9 1	1 2 6 1	1 1 5 1	1 2 2 1	1 0 1 1	1 1 8 1	1 2 3 1	1 4 1 1	1 1 3 1	1 3 0 1	1 3 5 1
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery														+											+
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx							+																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell carcinoma																									
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, uncertain primary site																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pheochromocytoma malignant																			X						
Pheochromocytoma benign				X																			X		
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																				X					
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X				X				X	X	X	X		X	X	X	X	X	X	X	X				X
Pars distalis, adenoma, multiple																									
Pars distalis, adenoma, two																									
Pars distalis, carcinoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
C cell, adenoma																									
C cell, carcinoma																									
Follicular cell, adenoma, papillary																									
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma						X																			
Polyp stromal																					X		X	X	
Vagina																									
Schwannoma malignant																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 300 ppm (Continued)

DAYS ON STUDY	728	728	728	729	729	729	729	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	TOTAL:
CARCASS ID	14551	14611	14811	15011	12811	13311	14011	14311	10901	11011	12111	12411	12511	12711	13811	13911	10211	10311	10611	10711	10811	11411	11711	11911	12011	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery					+		+							+											5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																								+		1
Squamous cell carcinoma																								X		1
Tooth								+																		1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, uncertain primary site																									X	1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Pheochromocytoma malignant																										1
Pheochromocytoma benign																						X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																							X			2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	M	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X						X	X		X		X	X				X		X			X		24
Pars distalis, adenoma, multiple										X																1
Pars distalis, adenoma, two						X											X	X							X	4
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																									X	1
C cell, adenoma														X		X										2
C cell, carcinoma													X				X									2
Follicular cell, adenoma, papillary						X																				1
Follicular cell, carcinoma													X													1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Adenoma					X																					2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Polyp stromal											X													X		5
Vagina									+																	1
Schwannoma malignant									X																	1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 300 ppm (Continued)

DAYS ON STUDY	414	434	444	456	499	506	526	576	576	582	606	614	626	637	646	680	681	683	690	697	709	709	714	718	728
CARCASS ID	10551	13111	10411	11111	11611	14911	14711	13411	13611	14411	11211	13211	14211	13711	12911	12611	11511	12211	10111	11811	12311	14111	11131	13001	13551
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X																
Adenoma		X																							
Fibroadenoma					X							X		X			X				X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, myxoma																						X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sternum, osteosarcoma																									
Skeletal muscle							+																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	M	M	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+							+	+	+							
Harderian gland																+	+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X							X		X	X	X			X	X	X			X	X	X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 300 ppm (Continued)

DAYS ON STUDY	728	728	728	729	729	729	729	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	TOTAL.
CARCASS ID	14501	14611	14811	15011	12811	13311	14011	14311	10911	11011	12111	12411	12511	12711	13811	13911	10211	10311	10611	10711	10811	11411	11711	11911	12011	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	M	+	M	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	37
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma				X																						2
Adenoma																										1
Fibroadenoma										X		X					X				X					9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																							X			1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, lipoma						X																				1
Subcutaneous tissue, myxoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sternum, osteosarcoma									X																	1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																								+		5
Harderian gland																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X		X		X		X	X			X	X	X	X	X			X		X			25

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

	Chamber Control	100 ppm	300 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	5/48 (10%)	(b) 0/14 (0%)	3/45 (7%)
Adjusted Rates (c)	14.3%		9.7%
Terminal Rates (d)	3/31 (10%)		1/23 (4%)
Day of First Observation	592		456
Life Table Test (e)			P=0.470N
Logistic Regression Test (e)			P=0.392N
Fisher Exact Test (e)			P=0.394N
Adrenal Medulla: Pheochromocytoma; Benign or Malignant			
Overall Rates (a)	7/48 (15%)	(b) 0/14 (0%)	4/45 (9%)
Adjusted Rates (c)	18.5%		12.5%
Terminal Rates (d)	3/31 (10%)		1/23 (4%)
Day of First Observation	545		456
Life Table Test (e)			P=0.373N
Logistic Regression Test (e)			P=0.292N
Fisher Exact Test (e)			P=0.300N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/48 (2%)	(b) 4/11 (36%)	12/46 (4%)
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	(b) 1/12 (8%)	3/49 (6%)
Adjusted Rates (c)	6.5%		9.6%
Terminal Rates (d)	2/31 (6%)		1/26 (4%)
Day of First Observation	728		680
Life Table Test (e)			P=0.439
Logistic Regression Test (e)			P=0.464
Fisher Exact Test (e)			P=0.490
Mammary Gland: Adenocarcinoma			
Overall Rates (f)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (c)	8.6%	0.0%	6.1%
Terminal Rates (d)	2/31 (6%)	0/28 (0%)	1/26 (4%)
Day of First Observation	592		576
Life Table Tests (e)	P=0.596N	P=0.136N	P=0.560N
Logistic Regression Tests (e)	P=0.546N	P=0.120N	P=0.499N
Cochran-Armitage Trend Test (e)	P=0.548N		
Fisher Exact Test (e)		P=0.121N	P=0.500N
Mammary Gland: Carcinoma or Adenocarcinoma			
Overall Rates (f)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (c)	8.6%	2.2%	6.1%
Terminal Rates (d)	2/31 (6%)	0/28 (0%)	1/26 (4%)
Day of First Observation	592	560	576
Life Table Tests (e)	P=0.547N	P=0.328N	P=0.560N
Logistic Regression Tests (e)	P=0.491N	P=0.317N	P=0.499N
Cochran-Armitage Trend Test (e)	P=0.500N		
Fisher Exact Test (e)		P=0.309N	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (f)	16/50 (32%)	8/50 (16%)	9/50 (18%)
Adjusted Rates (c)	42.3%	25.6%	26.4%
Terminal Rates (d)	10/31 (32%)	6/28 (21%)	4/26 (15%)
Day of First Observation	592	583	499
Life Table Tests (e)	P=0.194N	P=0.088N	P=0.176N
Logistic Regression Tests (e)	P=0.117N	P=0.048N	P=0.092N
Cochran-Armitage Trend Test (e)	P=0.103N		
Fisher Exact Test (e)		P=0.050N	P=0.083N

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

	Chamber Control	100 ppm	300 ppm
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (f)	16/50 (32%)	9/50 (18%)	10/50 (20%)
Adjusted Rates (c)	42.2%	29.0%	27.9%
Terminal Rates (d)	10/31 (32%)	7/28 (25%)	4/26 (15%)
Day of First Observation	592	583	434
Life Table Tests (e)	P=0.264N	P=0.135N	P=0.243N
Logistic Regression Tests (e)	P=0.162N	P=0.079N	P=0.131N
Cochran-Armitage Trend Test (e)	P=0.151N		
Fisher Exact Test (e)		P=0.083N	P=0.127N
Mammary Gland: Adenoma, Fibroadenoma, Carcinoma, or Adenocarcinoma			
Overall Rates (f)	18/50 (36%)	10/50 (20%)	12/50 (24%)
Adjusted Rates (c)	47.7%	30.6%	32.8%
Terminal Rates (d)	12/31 (39%)	7/28 (25%)	5/26 (19%)
Day of First Observation	592	560	434
Life Table Tests (e)	P=0.306N	P=0.106N	P=0.272N
Logistic Regression Tests (e)	P=0.183N	P=0.056N	P=0.144N
Cochran-Armitage Trend Test (e)	P=0.174N		
Fisher Exact Test (e)		P=0.059N	P=0.138N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	28/50 (56%)	26/43 (60%)	29/50 (58%)
Adjusted Rates (c)	71.2%	74.8%	71.2%
Terminal Rates (d)	20/31 (65%)	14/22 (64%)	15/26 (58%)
Day of First Observation	545	495	414
Life Table Tests (e)	P=0.269	P=0.243	P=0.259
Logistic Regression Tests (e)	P=0.437	P=0.379	P=0.444
Cochran-Armitage Trend Test (e)	P=0.501		
Fisher Exact Test (e)		P=0.412	P=0.500
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	4/50 (8%)	2/43 (5%)	1/50 (2%)
Adjusted Rates (c)	11.7%	9.1%	2.3%
Terminal Rates (d)	3/31 (10%)	2/22 (9%)	0/26 (0%)
Day of First Observation	592	728	576
Life Table Tests (e)	P=0.187N	P=0.485N	P=0.225N
Logistic Regression Tests (e)	P=0.152N	P=0.424N	P=0.179N
Cochran-Armitage Trend Test (e)	P=0.147N		
Fisher Exact Test (e)		P=0.413N	P=0.181N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	32/50 (64%)	28/43 (65%)	30/50 (60%)
Adjusted Rates (c)	79.5%	81.1%	71.9%
Terminal Rates (d)	23/31 (74%)	16/22 (73%)	15/26 (58%)
Day of First Observation	545	495	414
Life Table Tests (e)	P=0.426	P=0.305	P=0.423
Logistic Regression Tests (e)	P=0.432N	P=0.509	P=0.469N
Cochran-Armitage Trend Test (e)	P=0.369N		
Fisher Exact Test (e)		P=0.542	P=0.418N
Subcutaneous Tissue: Fibroma			
Overall Rates (f)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	7.2%	5.9%	3.1%
Terminal Rates (d)	0/31 (0%)	1/28 (4%)	0/26 (0%)
Day of First Observation	434	637	690
Life Table Tests (e)	P=0.285N	P=0.516N	P=0.338N
Logistic Regression Tests (e)	P=0.245N	P=0.551N	P=0.303N
Cochran-Armitage Trend Test (e)	P=0.252N		
Fisher Exact Test (e)		P=0.500N	P=0.309N

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

	Chamber Control	100 ppm	300 ppm
Subcutaneous Tissue: Fibroma or Myxoma			
Overall Rates (f)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	7.2%	5.9%	6.4%
Terminal Rates (d)	0/31 (0%)	1/28 (4%)	0/26 (0%)
Day of First Observation	434	637	690
Life Table Tests (e)	P=0.497N	P=0.516N	P=0.535N
Logistic Regression Tests (e)	P=0.447N	P=0.551N	P=0.494N
Cochran-Armitage Trend Test (e)	P=0.459N		
Fisher Exact Test (e)		P=0.500N	P=0.500N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (f)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (c)	10.2%	8.7%	6.9%
Terminal Rates (d)	1/31 (3%)	1/28 (4%)	1/26 (4%)
Day of First Observation	434	637	690
Life Table Tests (e)	P=0.345N	P=0.524N	P=0.393N
Logistic Regression Tests (e)	P=0.282N	P=0.528N	P=0.329N
Cochran-Armitage Trend Test (e)	P=0.291N		
Fisher Exact Test (e)		P=0.500N	P=0.339N
Subcutaneous Tissue: Fibroma, Myxoma, or Fibrosarcoma			
Overall Rates (f)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (c)	10.2%	8.7%	10.0%
Terminal Rates (d)	1/31 (3%)	1/28 (4%)	1/26 (4%)
Day of First Observation	434	637	690
Life Table Tests (e)	P=0.523N	P=0.524N	P=0.556N
Logistic Regression Tests (e)	P=0.456N	P=0.528N	P=0.492N
Cochran-Armitage Trend Test (e)	P=0.465N		
Fisher Exact Test (e)		P=0.500N	P=0.500N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	(b) 0/10 (0%)	2/50 (4%)
Adjusted Rates (c)	19.4%		7.7%
Terminal Rates (d)	4/31 (13%)		2/26 (8%)
Day of First Observation	592		728
Life Table Test (e)			P=0.124N
Logistic Regression Test (e)			P=0.091N
Fisher Exact Test (e)			P=0.080N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	(b) 0/10 (0%)	4/50 (8%)
Adjusted Rates (c)	19.4%		15.4%
Terminal Rates (d)	4/31 (13%)		4/26 (15%)
Day of First Observation	592		728
Life Table Test (e)			P=0.354N
Logistic Regression Test (e)			P=0.294N
Fisher Exact Test (e)			P=0.262N
Uterus: Stromal Polyp			
Overall Rates (f)	7/50 (14%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (c)	19.3%	19.6%	17.1%
Terminal Rates (d)	4/31 (13%)	5/28 (18%)	2/26 (8%)
Day of First Observation	434	526	709
Life Table Tests (e)	P=0.441N	P=0.555N	P=0.476N
Logistic Regression Tests (e)	P=0.365N	P=0.499N	P=0.401N
Cochran-Armitage Trend Test (e)	P=0.344N		
Fisher Exact Test (e)		P=0.500N	P=0.380N

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

	Chamber Control	100 ppm	300 ppm
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	20/50 (40%)	16/50 (32%)	25/50 (50%)
Adjusted Rates (c)	46.9%	36.5%	66.5%
Terminal Rates (d)	9/31 (29%)	3/28 (11%)	14/26 (54%)
Day of First Observation	582	421	444
Life Table Tests (e)	P=0.084	P=0.346N	P=0.121
Logistic Regression Tests (e)	P=0.129	P=0.279N	P=0.188
Cochran-Armitage Trend Test (e)	P=0.124		
Fisher Exact Test (e)		P=0.266N	P=0.211

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

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE

	Chamber Control	100 ppm	300 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	16	21	18
Natural death	3	1	6
Survivors			
Terminal sacrifice	31	28	26
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(5)	(46)
Inflammation, chronic			1 (2%)
Inflammation, chronic active	1 (2%)		
Parasite metazoan	2 (4%)		8 (17%)
Artery, inflammation, chronic, focal	1 (2%)		
Intestine large, colon	(50)	(10)	(49)
Parasite metazoan	7 (14%)	1 (10%)	9 (18%)
Muscularis, atrophy, focal	1 (2%)		
Intestine large, rectum	(46)	(9)	(46)
Parasite metazoan	2 (4%)		3 (7%)
Mucosa, inflammation, chronic active, multifocal	1 (2%)		
Intestine small, duodenum	(50)	(9)	(50)
Muscularis, fibrosis, focal			1 (2%)
Intestine small, ileum	(48)	(7)	(48)
Inflammation, chronic, diffuse	1 (2%)		
Parasite metazoan			1 (2%)
Liver	(50)	(33)	(50)
Angiectasis, focal	3 (6%)		3 (6%)
Angiectasis, multifocal		2 (6%)	1 (2%)
Basophilic focus	8 (16%)	3 (9%)	7 (14%)
Basophilic focus, multiple	19 (38%)	9 (27%)	14 (28%)
Clear cell focus	1 (2%)		
Congestion, acute, multifocal		3 (9%)	
Cytomegaly, multifocal	1 (2%)		1 (2%)
Cytoplasmic alteration, focal	1 (2%)		1 (2%)
Eosinophilic focus	1 (2%)		
Fatty change, diffuse	3 (6%)	1 (3%)	
Fatty change, focal			2 (4%)
Fatty change, multifocal	7 (14%)	1 (3%)	4 (8%)
Fibrosis, multifocal	1 (2%)		
Granuloma, multifocal	19 (38%)	6 (18%)	14 (28%)
Hemorrhage, acute, multifocal			1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	5 (15%)	6 (12%)
Hepatodiaphragmatic nodule, multiple	1 (2%)	1 (3%)	
Hyperplasia, nodular, focal		2 (6%)	
Hyperplasia, nodular, multifocal	1 (2%)		2 (4%)
Inflammation, chronic, multifocal			1 (2%)
Mitotic alteration		1 (3%)	1 (2%)
Mixed cell focus	1 (2%)		3 (6%)
Mixed cell focus, two			1 (2%)
Necrosis, focal	1 (2%)	1 (3%)	
Necrosis, multifocal	8 (16%)	1 (3%)	5 (10%)
Pigmentation, multifocal		1 (3%)	
Bile duct, hyperplasia, focal	1 (2%)		
Bile duct, hyperplasia, multifocal	6 (12%)	7 (21%)	6 (12%)
Centrilobular, atrophy, multifocal	1 (2%)	1 (3%)	
Centrilobular, degeneration, diffuse	1 (2%)	4 (12%)	
Centrilobular, degeneration, multifocal		1 (3%)	
Centrilobular, fatty change, diffuse	4 (8%)	3 (9%)	5 (10%)
Centrilobular, fatty change, multifocal			1 (2%)
Centrilobular, necrosis, diffuse			1 (2%)
Centrilobular, necrosis, multifocal	1 (2%)		3 (6%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (Continued)

	Chamber Control	100 ppm	300 ppm
ALIMENTARY SYSTEM			
Liver (Continued)	(50)	(33)	(50)
Periportal, fatty change, multifocal		2 (6%)	
Portal, inflammation, chronic, multifocal			1 (2%)
Mesentery	(4)	(2)	(5)
Artery, inflammation, necrotizing, multifocal			1 (20%)
Fat, inflammation, necrotizing, focal			1 (20%)
Fat, necrosis, focal	1 (25%)		4 (80%)
Pancreas	(50)	(13)	(49)
Inflammation, granulomatous, focal			1 (2%)
Acinus, atrophy, diffuse	2 (4%)		
Acinus, atrophy, focal	1 (2%)		2 (4%)
Acinus, atrophy, multifocal	13 (26%)	3 (23%)	8 (16%)
Acinus, hyperplasia, focal	1 (2%)		
Artery, inflammation, chronic, focal	2 (4%)		
Artery, inflammation, chronic active, multifocal	1 (2%)		
Duct, cyst, multiple			1 (2%)
Interlobular, inflammation, chronic, diffuse	1 (2%)		
Pharynx			(1)
Mucosa, palate, inflammation, chronic, diffuse			1 (100%)
Salivary glands	(50)	(9)	(47)
Inflammation, chronic, diffuse	1 (2%)		
Inflammation, chronic active, focal	1 (2%)		
Duct, inflammation, chronic active, focal	1 (2%)		
Parotid gland, inflammation, chronic active, focal			1 (2%)
Stomach, forestomach	(49)	(11)	(49)
Inflammation, chronic active	3 (6%)	1 (9%)	1 (2%)
Ulcer, subacute, single	1 (2%)		
Epithelium, hyperplasia	2 (4%)	1 (9%)	1 (2%)
Stomach, glandular	(50)	(11)	(50)
Cyst epithelial inclusion		1 (9%)	
Inflammation, chronic active	1 (2%)		
Mucosa, cyst, multiple	2 (4%)		
Tooth			(1)
Peridontal tissue, inflammation, chronic, diffuse			1 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(10)	(50)
Abscess, single	1 (2%)		
Cardiomyopathy	36 (72%)	4 (40%)	40 (80%)
Artery, inflammation, chronic active, focal			1 (2%)
Artery, inflammation, chronic active, multifocal	1 (2%)		
Atrium left, thrombus	2 (4%)	1 (10%)	2 (4%)
Epicardium, inflammation, chronic active, focal			1 (2%)
Myocardium, degeneration, focal			1 (2%)
Valve, degeneration, mucoid, multifocal	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(14)	(50)
Bilateral, capsule, fibrosis, multifocal			1 (2%)
Capsule, accessory adrenal cortical nodule	5 (10%)	1 (7%)	5 (10%)
Adrenal gland, cortex	(50)	(14)	(50)
Angiectasis, focal	2 (4%)		
Angiectasis, multifocal	4 (8%)	3 (21%)	4 (8%)
Atrophy			1 (2%)
Congestion	4 (8%)	1 (7%)	2 (4%)
Degeneration, fatty, diffuse	1 (2%)		1 (2%)
Degeneration, fatty, focal	8 (16%)	1 (7%)	8 (16%)
Degeneration, fatty, multifocal	2 (4%)	1 (7%)	1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (Continued)

	Chamber Control	100 ppm	300 ppm
ENDOCRINE SYSTEM			
Adrenal gland, cortex (Continued)	(50)	(14)	(50)
Hyperplasia, focal	9 (18%)		2 (4%)
Hyperplasia, multifocal		1 (7%)	1 (2%)
Hypertrophy, focal	4 (8%)		1 (2%)
Hypertrophy, multifocal	2 (4%)	1 (7%)	1 (2%)
Pigmentation, hemosiderin, diffuse	2 (4%)		1 (2%)
Pigmentation, hemosiderin, multifocal			1 (2%)
Adrenal gland, medulla	(48)	(14)	(45)
Angiectasis, multifocal	1 (2%)		1 (2%)
Hyperplasia, focal	5 (10%)	1 (7%)	5 (11%)
Hyperplasia, multifocal	2 (4%)		3 (7%)
Vacuolization cytoplasmic, diffuse	1 (2%)		
Islets, pancreatic	(50)	(12)	(49)
Ectopic tissue, focal	1 (2%)		
Hyperplasia, focal			4 (8%)
Hyperplasia, multifocal	2 (4%)		
Hypertrophy, focal	2 (4%)		1 (2%)
Hypoplasia, diffuse	1 (2%)		
Pituitary gland	(50)	(43)	(50)
Pars distalis, angiectasis, focal	4 (8%)	1 (2%)	2 (4%)
Pars distalis, angiectasis, multifocal	2 (4%)	3 (7%)	
Pars distalis, concretion			1 (2%)
Pars distalis, cyst	5 (10%)	10 (23%)	10 (20%)
Pars distalis, cyst, multiple		1 (2%)	
Pars distalis, hemorrhage, chronic, focal	1 (2%)		
Pars distalis, hyperplasia	1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal	3 (6%)	2 (5%)	2 (4%)
Pars distalis, hyperplasia, multifocal		1 (2%)	1 (2%)
Pars distalis, pigmentation, hemosiderin, diffuse	1 (2%)		
Pars intermedia, pigmentation, hemosiderin, diffuse	1 (2%)		
Pars nervosa, pigmentation, diffuse			1 (2%)
Thyroid gland	(50)	(10)	(50)
Cyst	2 (4%)		1 (2%)
Developmental malformation		1 (10%)	
C-cell, hyperplasia, focal	2 (4%)		3 (6%)
C-cell, hyperplasia, multifocal	21 (42%)	1 (10%)	7 (14%)
GENERAL BODY SYSTEM			
Tissue, NOS		(1)	
Necrosis, acute		1 (100%)	
GENITAL SYSTEM			
Clitoral gland	(48)	(11)	(46)
Abscess		1 (9%)	
Atrophy		1 (9%)	1 (2%)
Ectasia		2 (18%)	4 (9%)
Hyperplasia	3 (6%)	1 (9%)	3 (7%)
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, chronic active	1 (2%)	1 (9%)	2 (4%)
Inflammation, granulomatous	2 (4%)		3 (7%)
Ovary	(50)	(18)	(50)
Angiectasis, multifocal	1 (2%)		
Congestion, diffuse	1 (2%)		1 (2%)
Cyst		5 (28%)	3 (6%)
Hyperplasia	1 (2%)		

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (Continued)

	Chamber Control	100 ppm	300 ppm
GENITAL SYSTEM (Continued)			
Uterus	(50)	(18)	(50)
Adenomyosis, focal			1 (2%)
Cyst	1 (2%)		1 (2%)
Dilatation	1 (2%)	3 (17%)	2 (4%)
Inflammation, acute, multifocal	1 (2%)		
Inflammation, chronic active	1 (2%)		1 (2%)
Endometrium, hyperplasia, focal	1 (2%)		
Epithelium, hyperplasia, diffuse	1 (2%)		1 (2%)
Epithelium, hyperplasia, focal	2 (4%)		1 (2%)
Lumen, hemorrhage		1 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(9)	(50)
Hyperplasia	2 (4%)		3 (6%)
Hyperplasia, megakaryocyte			1 (2%)
Metaplasia, osseous, diffuse	1 (2%)		
Myeloid cell, hyperplasia	6 (12%)		2 (4%)
Lymph node	(50)	(17)	(50)
Hyperplasia, re cell	1 (2%)		
Mediastinal, hemorrhage	4 (8%)		3 (6%)
Mediastinal, hyperplasia, re cell			1 (2%)
Mediastinal, pigmentation, hemosiderin, diffuse			1 (2%)
Pancreatic, hemorrhage	1 (2%)	1 (6%)	
Pancreatic, inflammation, acute		1 (6%)	
Pancreatic, pigmentation, hemosiderin			1 (2%)
Renal, hyperplasia, plasma cell			1 (2%)
Renal, hyperplasia, re cell			1 (2%)
Lymph node, mandibular	(47)	(11)	(47)
Edema			1 (2%)
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, plasma cell	2 (4%)		5 (11%)
Hyperplasia, re cell		1 (9%)	1 (2%)
Artery, inflammation, chronic active, focal			1 (2%)
Lymph node, mesenteric	(47)	(12)	(46)
Hemorrhage	3 (6%)	3 (25%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)		
Hyperplasia, re cell	4 (9%)		3 (7%)
Pigmentation, hemosiderin		1 (8%)	
Spleen	(50)	(19)	(50)
Fibrosis, focal		1 (5%)	2 (4%)
Fibrosis, multifocal			1 (2%)
Granuloma, multifocal	1 (2%)		
Hematopoietic cell proliferation	5 (10%)		5 (10%)
Hyperplasia, reticulum cell, multifocal	1 (2%)		
Metaplasia, osseous, focal		1 (5%)	
Pigmentation, hemosiderin	11 (22%)	1 (5%)	15 (30%)
Capsule, ectopic tissue	1 (2%)		
Capsule, infiltration cellular, lymphocytic, multifocal	1 (2%)		
Thymus	(38)	(6)	(37)
Ectopic parathyroid gland	1 (3%)	2 (33%)	
Hyperplasia, tubular, diffuse	6 (16%)		14 (38%)
Infiltration cellular, polymorphonuclear	1 (3%)		
Artery, mediastinum, inflammation, chronic active, multifocal	1 (3%)		

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (Continued)

	Chamber Control	100 ppm	300 ppm
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(29)	(49)
Ectasia, diffuse		3 (10%)	1 (2%)
Ectasia, focal	2 (4%)		2 (4%)
Ectasia, multifocal	12 (25%)	10 (34%)	15 (31%)
Galactocele		1 (3%)	
Hyperplasia, diffuse	14 (29%)	11 (38%)	15 (31%)
Hyperplasia, focal	1 (2%)	1 (3%)	2 (4%)
Hyperplasia, multifocal	4 (8%)		
Inflammation, granulomatous, multifocal	2 (4%)		
Artery, inflammation, chronic active, focal			1 (2%)
Skin	(50)	(13)	(50)
Hyperplasia, squamous, focal			1 (2%)
Inflammation, chronic active, focal			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(49)	(9)	(50)
Hyperostosis	1 (2%)		2 (4%)
Osteopetrosis	1 (2%)		5 (10%)
Skeletal muscle			(1)
Inflammation, proliferative, diffuse			1 (100%)
NERVOUS SYSTEM			
Brain	(50)	(11)	(50)
Compression	11 (22%)	1 (9%)	16 (32%)
Hemorrhage, focal	2 (4%)		
Hemorrhage, multifocal	1 (2%)	1 (9%)	
Hydrocephalus	2 (4%)	1 (9%)	5 (10%)
RESPIRATORY SYSTEM			
Larynx	(46)	(6)	(40)
Hyperplasia, papillary, focal			1 (3%)
Inflammation, acute, diffuse			1 (3%)
Inflammation, acute, focal	1 (2%)		
Inflammation, chronic, diffuse	1 (2%)		
Inflammation, chronic, focal	4 (9%)		3 (8%)
Inflammation, chronic active, focal	10 (22%)		4 (10%)
Submucosa, dilatation, multifocal	1 (2%)		
Lung	(50)	(50)	(50)
Atelectasis, focal			1 (2%)
Autolysis	1 (2%)		
Granuloma, multifocal		1 (2%)	
Hemorrhage, acute, multifocal	1 (2%)		
Inflammation, chronic, multifocal			1 (2%)
Alveolar epithelium, hyperplasia, focal		5 (10%)	1 (2%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)	
Alveolus, infiltration cellular, histiocytic, focal		1 (2%)	
Bronchiole, alveolus, inflammation, acute, multifocal			1 (2%)
Interstitium, inflammation, chronic, focal	2 (4%)		
Interstitium, inflammation, chronic, multifocal	1 (2%)	1 (2%)	1 (2%)
Peribronchial, hyperplasia, lymphoid, multifocal	2 (4%)		
Pleura, inflammation, subacute, multifocal			1 (2%)
Nose	(50)	(49)	(50)
Lumen, exudate	1 (2%)	4 (8%)	2 (4%)
Lumen, foreign body	2 (4%)		1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE (Continued)

	Chamber Control	100 ppm	300 ppm
RESPIRATORY SYSTEM			
Nose (Continued)	(50)	(49)	(50)
Mucosa, inflammation, acute			1 (2%)
Mucosa, inflammation, chronic	2 (4%)	2 (4%)	1 (2%)
Mucosa, inflammation, chronic active	1 (2%)	4 (8%)	4 (8%)
Mucosa, metaplasia, focal	1 (2%)		
Mucosa, thrombus, multifocal	2 (4%)	4 (8%)	
Nasolacrimal duct, exudate	5 (10%)	3 (6%)	4 (8%)
Nasolacrimal duct, inflammation, chronic	13 (26%)	17 (35%)	16 (32%)
Nasolacrimal duct, inflammation, chronic active	5 (10%)	1 (2%)	4 (8%)
Olfactory epithelium, atrophy		2 (4%)	3 (6%)
Olfactory epithelium, cyst		5 (10%)	13 (26%)
Olfactory epithelium, erosion		3 (6%)	4 (8%)
Olfactory epithelium, exudate		1 (2%)	
Olfactory epithelium, hyperplasia, eosinophil	2 (4%)	9 (18%)	21 (42%)
Olfactory epithelium, metaplasia		1 (2%)	
Respiratory epithelium, cyst		6 (12%)	10 (20%)
Respiratory epithelium, hyperplasia	7 (14%)	19 (39%)	16 (32%)
Respiratory epithelium, hyperplasia, eosinophil			3 (6%)
Respiratory epithelium, hyperplasia, multifocal	1 (2%)		
Trachea	(50)	(8)	(50)
Inflammation, acute, focal	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
SPECIAL SENSES SYSTEM			
Eye	(2)	(3)	(5)
Cataract	1 (50%)		1 (20%)
Bilateral, cataract		1 (33%)	1 (20%)
Bilateral, retina, degeneration		1 (33%)	
Retina, degeneration	1 (50%)		1 (20%)
Harderian gland			(2)
Inflammation, chronic, multifocal			2 (100%)
URINARY SYSTEM			
Kidney	(50)	(14)	(50)
Hydronephrosis			1 (2%)
Nephropathy, chronic	46 (92%)	6 (43%)	43 (86%)
Pigmentation, diffuse	8 (16%)	2 (14%)	11 (22%)
Pigmentation, multifocal	11 (22%)	1 (7%)	6 (12%)
Bilateral, hydronephrosis			1 (2%)
Cortex, cyst	1 (2%)		
Cortex, hyperplasia, atypical, focal	2 (4%)		1 (2%)
Cortex, inflammation, suppurative, focal	1 (2%)		
Cortex, mineralization, multifocal			1 (2%)
Corticomedullary junction, mineralization, multifocal			1 (2%)
Pelvis, inflammation, suppurative, diffuse			1 (2%)
Proximal convoluted renal tubule, necrosis, multifocal	2 (4%)		
Transitional epithelium, hyperplasia			3 (6%)
Transitional epithelium, mineralization, focal	1 (2%)		1 (2%)
Transitional epithelium, mineralization, multifocal	3 (6%)		3 (6%)
Urinary bladder	(49)	(9)	(46)
Ectasia			2 (4%)
Inflammation, chronic, diffuse			1 (2%)
Artery, inflammation, chronic active, multifocal			1 (2%)
Transitional epithelium, hyperplasia, focal			1 (2%)

APPENDIX C

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

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

	Chamber Control	10 ppm	25 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	10	13	4
Natural death	6	7	2
Accidentally killed	1		1
Dosing accident			2
Survivors			
Terminal sacrifice	33	30	41
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(9)	(48)
Intestine large, cecum	(46)	(7)	(44)
Intestine large, colon	(48)	(10)	(47)
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Intestine small, duodenum	(47)	(10)	(49)
Polyp adenomatous		1 (10%)	1 (2%)
Intestine small, jejunum	(46)	(10)	(44)
Adenocarcinoma		1 (10%)	
Liver	(50)	(23)	(48)
Hemangiosarcoma, multiple	1 (2%)		
Hepatocellular carcinoma	9 (18%)	11 (48%)	7 (15%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (4%)	5 (10%)
Hepatocellular adenoma	6 (12%)	2 (9%)	2 (4%)
Hepatocellular adenoma, multiple	2 (4%)		
Sarcoma, metastatic, uncertain primary site			1 (2%)
Mesentery	(6)		(3)
Fat, hemangiosarcoma			1 (33%)
Pancreas	(49)	(9)	(49)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Salivary glands	(50)	(11)	(50)
Stomach, forestomach	(48)	(10)	(47)
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(10)	(48)
Capsule, adenoma, multiple	1 (2%)		
Capsule, sarcoma, metastatic, uncertain primary site			1 (2%)
Adrenal gland, cortex	(49)	(10)	(48)
Adenoma	1 (2%)		
Adrenal gland, medulla	(49)	(9)	(47)
Pheochromocytoma benign	1 (2%)		1 (2%)
Islets, pancreatic	(49)	(9)	(49)
Adenoma			2 (4%)
Parathyroid gland	(36)	(6)	(35)
Pituitary gland	(45)	(11)	(47)
Pars distalis, adenoma	1 (2%)		1 (2%)
Thyroid gland	(49)	(9)	(47)
Follicular cell, adenocarcinoma	1 (2%)		
Follicular cell, adenoma	3 (6%)		

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

	Chamber Control	10 ppm	25 ppm
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(49)	(11)	(49)
Prostate	(46)	(9)	(44)
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Seminal vesicle	(48)	(17)	(49)
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Testes	(50)	(12)	(49)
Interstitial cell, adenoma		1 (8%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(10)	(49)
Lymph node	(50)	(26)	(50)
Lymph node, mandibular	(47)	(11)	(35)
Lymph node, mesenteric	(42)	(19)	(33)
Spleen	(49)	(14)	(49)
Hemangiosarcoma		1 (7%)	
Capsule, sarcoma, metastatic, uncertain primary site			1 (2%)
Thymus	(35)	(6)	(34)
INTEGUMENTARY SYSTEM			
Skin	(50)	(30)	(49)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, fibrous histiocytoma		1 (3%)	
Subcutaneous tissue, hemangioma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(10)	(50)
Osteoma	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(11)	(50)
Meninges, hamartoma	1 (2%)		
RESPIRATORY SYSTEM			
Larynx	(44)	(6)	(46)
Lung	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	9 (18%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma, multiple	2 (4%)	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)	4 (8%)	
SPECIAL SENSES SYSTEM			
Harderian gland		(1)	
Bilateral, adenoma		1 (100%)	
URINARY SYSTEM			
Kidney	(49)	(11)	(50)
Urinary bladder	(49)	(27)	(47)

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

	Chamber Control	10 ppm	25 ppm
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic	2 (4%)	2 (4%)	
Lymphoma malignant lymphocytic	3 (6%)		
Lymphoma malignant mixed	2 (4%)	1 (2%)	
TUMOR SUMMARY			
Total animals with primary neoplasms **	33	23	20
Total primary neoplasms	48	28	25
Total animals with benign neoplasms	21	7	10
Total benign neoplasms	26	7	11
Total animals with malignant neoplasms	18	16	13
Total malignant neoplasms	22	21	14
Total animals with secondary neoplasms ***	3	4	1
Total secondary neoplasms	3	4	7
Total animals with malignant neoplasms--uncertain primary site			1

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

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

DAYS ON STUDY	266	514	529	567	588	607	644	648	658	670	673	673	687	696	707	714	717	731	731	732	732	732	732	732	732
CARCASS ID	721	981	631	551	971	701	811	951	741	571	511	661	531	561	881	901	521	731	891	541	581	591	601	691	711
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	M	+	M	+	A	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	M	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	M	+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+		+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	A	+	+		M		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+		+		+	+	+	+	+	+		+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple			X																						
Hepatocellular carcinoma		X		X	X				X	X									X			X			
Hepatocellular carcinoma, multiple											X														
Hepatocellular adenoma					X																				
Hepatocellular adenoma, multiple																									
Mesentery					+					+	+		+	+											
Pancreas	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+		+	+		+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma, multiple																									
Adrenal gland, cortex	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																					X				
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pars distalis, adenoma																					X				
Thyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenocarcinoma					X																				
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland											+														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+									+	+	+						+	+	+		+	
Prostate	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+
Seminal vesicle	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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

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

DAYS ON STUDY	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	734	734	734	734	735	735	735	TOTAL:
CARCASS ID	7511	8411	8511	8611	8711	0001	6411	6511	6711	6811	7911	8011	8211	8311	9611	9911	6221	7711	7811	9311	9411	6111	7611	9111	9211	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	41
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma				X									X													9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma							X		X	X								X		X						6
Hepatocellular adenoma, multiple		X						X																		2
Mesentery																							+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma, multiple								X																		1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	M	36
Pituitary gland	+	I	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenocarcinoma																										1
Follicular cell, adenoma														X							X		X			3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Preputial gland		+							+											+	+				+	15
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

DAYS ON STUDY	266	514	529	567	588	607	644	648	658	670	673	673	687	696	707	714	717	731	731	732	732	732	732	732	732
CARCASS ID	721	981	631	551	971	701	811	951	741	571	511	661	531	561	881	901	521	731	891	541	581	591	601	691	711
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	M	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	M	+	M	A	M	+,	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	+	+	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, hamartoma												X													
RESPIRATORY SYSTEM																									
Larynx	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X		X	X		X	X	X					
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple														X											
Hepatocellular carcinoma, metastatic, liver				X							X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+																					
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																				X					
Lymphoma malignant lymphocytic																							X		
Lymphoma malignant mixed										X															

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

DAYS ON STUDY	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	TOTAL
CARCASS ID	7 5 1	8 4 1	8 5 1	8 6 1	8 7 1	0 0 1	6 4 1	6 5 1	6 7 1	6 8 1	7 9 1	8 0 1	8 2 1	8 3 1	9 6 1	9 9 1	6 2 1	7 7 1	7 8 1	9 3 1	9 4 1	6 1 1	7 6 1	9 1 1	9 2 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	+	M	+	+	35
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	+	M	+	M	M	M	M	M	M	+	M	+	M	M	M	M	+	+	+	M	M	11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, hamartoma																										1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	44
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X				X				X																	9
Alveolar/bronchiolar carcinoma																						X				1
Alveolar/bronchiolar carcinoma, multiple																							X			2
Hepatocellular carcinoma, metastatic, liver				X																						3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear					+																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic													X	X												2
Lymphoma malignant lymphocytic										X													X			3
Lymphoma malignant mixed																										2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 10 ppm

DAYS ON STUDY	3 5 8	3 9 2	4 3 4	5 5 0	5 5 3	5 6 7	5 7 4	5 8 2	6 0 2	6 2 3	6 2 3	6 3 2	6 6 1	6 7 6	6 7 6	6 8 2	6 8 6	6 9 5	7 1 4	7 2 4	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2
CARCASS ID	2 6 5 1	2 7 6 1	2 6 8 1	2 9 2 1	2 5 5 1	2 5 3 1	2 5 9 1	2 9 3 1	2 8 7 1	2 5 1 1	2 7 7 1	2 5 8 1	2 9 5 1	2 6 0 1	2 8 1 1	2 8 8 1	2 9 9 1	2 9 1 1	2 7 3 1	2 5 7 1	2 5 4 1	2 5 6 1	2 5 2 1	2 7 1 1	2 7 2 1
ALIMENTARY SYSTEM																									
Esophagus	M		+	+		+	+	+	M	+	+	+								+					
Gallbladder	M			+		+	+	+	A	+	+	+		+		A		+		+					
Intestine large	+		+	+		+	+	+	+	+	+	+								+					
Intestine large, cecum	+		A	M		+	+	+	A	M	+	+								+					
Intestine large, colon	+		+	+		+	+	+	A	+	+	+								+					
Intestine large, rectum	M		A	+		+	+	+	A	+	+	+								+					
Intestine small	+		+	+		+	+	+	+	+	+	+						+		+					
Intestine small, duodenum	+		A	+		+	+	M	A	+	+	+						+		+					
Polyp adenomatous																		X							
Intestine small, ileum	+		A	+		+	+	+	M	+	+	+								+					
Intestine small, jejunum	+		A	+		+	+	+	M	+	M	+								+					
Adenocarcinoma																									
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+			+		+		+			+		
Hepatocellular carcinoma			X		X	X					X	X				X				X			X		
Hepatocellular carcinoma, multiple							X																		
Hepatocellular adenoma																									
Pancreas	+		A	+		+	+	+	A	+	+	+								+					
Salivary glands	+		+	+		+	+	+	+	+	+	+								+					
Stomach	+	+	+	+		+	+	+	A	+	+	+							+	+					
Stomach, forestomach	+	A	+	+		+	+	+	A	+	+	+								+					
Stomach, glandular	+	A	+	+		+	+	+	A	+	+	+							+	+					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+		+	+	+	+	+	+	+								+					
ENDOCRINE SYSTEM																									
Adrenal gland	+		+	+		+	+	+	A	+	+	+								+					
Adrenal gland, cortex	+		+	+		+	+	+	A	+	+	+								+					
Adrenal gland, medulla	+		+	+		+	+	+	A	+	+	+								M					
Islets, pancreatic	+		A	+		+	+	+	A	+	+	+								+					
Parathyroid gland	M	A	+	+		M	+	+	M	M	+	+								M					
Pituitary gland	+		+	+		+	+	+	+	+	+	+								+					
Thyroid gland	M	A	+	+		+	+	+	M	+	+	+								+					
GENERAL BODY SYSTEM																									
Tissue, NOS																				+					
GENITAL SYSTEM																									
Epididymis	+	A	+	+		+	+	+	+	+	+	+								+					
Preputial gland				+					A														+		
Prostate	+		+	+		+	+	+	A	M	+	+								+					
Seminal vesicle	M		+	+	+	+	+	+	+	+	+	+	+	+	+				+	+					
Testes	+	A	+	+		+	+	+	+	+	+	+								+					
Interstitial cell, adenoma																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 ppm (Continued)

DAYS ON STUDY	732	732	732	732	733	733	733	733	733	733	733	733	733	734	734	734	734	734	735	735	735	735	735	735	735	TOTAL: TISSUES TUMORS
CARCASS ID	27441	27551	28991	29001	26991	27001	28831	28441	28551	28861	29711	29981	30001	26661	26671	28001	28221	29611	26111	26221	26331	26441	27881	27991	29411	
ALIMENTARY SYSTEM																										
Esophagus																										9
Gallbladder																										10
Intestine large																										11
Intestine large, cecum																										7
Intestine large, colon																										10
Intestine large, rectum																										8
Intestine small		+								+									+							15
Intestine small, duodenum																			+							10
Polyp adenomatous																										1
Intestine small, ileum																			+							10
Intestine small, jejunum										+									+							10
Adenocarcinoma										X																1
Liver				+	+			+						+			+		+					+		23
Hepatocellular carcinoma								X						X			X									11
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X	X																					2
Pancreas																										9
Salivary glands																										11
Stomach																										12
Stomach, forestomach																										10
Stomach, glandular																										11
CARDIOVASCULAR SYSTEM																										
Heart															+											13
ENDOCRINE SYSTEM																										
Adrenal gland																										10
Adrenal gland, cortex																										10
Adrenal gland, medulla																										9
Islets, pancreatic																										9
Parathyroid gland																										6
Pituitary gland																										11
Thyroid gland																										9
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Epididymis																										11
Preputial gland	+		+												+	+										6
Prostate																										9
Seminal vesicle		+		+																						17
Testes													+													12
Interstitial cell, adenoma													X													1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 ppm (Continued)

DAYS ON STUDY	358	392	434	550	553	567	574	582	602	623	623	632	661	676	676	682	686	695	714	724	731	731	732	732	732
CARCASS ID	26511	27611	26811	29211	25511	25311	25911	29311	28711	25111	27711	25811	29511	26011	28111	28811	29911	29911	27311	25711	25411	25611	25211	27111	27211
HEMATOPOIETIC SYSTEM																									
Bone marrow	M		+	+		+	+	+	+	+	+	+								+						
Lymph node	+		+	+		+	+	+	+	+	+	+	+					+		+			+	+	
Lymph node, mandibular	+		M	+		+	+	M	+	M	+	+								+					
Lymph node, mesenteric	M		M	+		+	+	+	M	+	+	+						+		+				+	
Spleen	+		A	+		+	+	+	A	+	+	+						+		+	+		+		
Hemangiosarcoma																					X				
Thymus	M		M	+		+	+	+	A	+	M	M								M					
INTEGUMENTARY SYSTEM																									
Mammary gland	M		M	M		M	M	M	M	+	+	M								M					
Skin	+	A	+	+		+	+	+	+	+	+	+		+	+			+	+	+	+				
Subcutaneous tissue, fibrous histiocytoma																					X				
MUSCULOSKELETAL SYSTEM																									
Bone	M		+	+		+	+	+	+	+	+	+								+					
Skeletal muscle								+																	
NERVOUS SYSTEM																									
Brain	+		+	+		+	+	+	+	+	+	+								+					
RESPIRATORY SYSTEM																									
Larynx	M		M	+		+	M	+		M	+	+								+					
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple	X																								
Hepatocellular carcinoma, metastatic, liver							X									X									
Nose	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	M	A	+	+		+	+	+	M	+	+	+								+					
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Bilateral, adenoma																									
URINARY SYSTEM																									
Kidney	+	A	+	+		+	+	+	A	+	+	+								+					
Urinary bladder	+		+	+	+	+	+	+	A	+	+	+	+	+	+		+	+	+	+				+	
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic												X											X		
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 ppm (Continued)

DAYS ON STUDY	732	732	732	732	733	733	733	733	733	733	733	733	733	734	734	734	734	734	735	735	735	735	735	735	735	TOTAL.
CARCASS ID	27411	27511	28911	29001	26691	27001	28311	28411	28511	28611	29711	29811	30011	26611	26711	28011	28211	29611	26111	26211	26311	26411	27811	27911	29411	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										10
Lymph node		+	+	+	+					+				+		+	+		+			+		+		26
Lymph node, mandibular		+														+	+									11
Lymph node, mesenteric		+			+					+				+		+	+		+			+		+		19
Spleen		+						+																		14
Hemangiosarcoma																										1
Thymus				+																						6
INTEGUMENTARY SYSTEM																										
Mammary gland																										2
Skin	+				+	+	+	+	+	+		+	+	+	+		+			+	+					30
Subcutaneous tissue, fibrous histiocytoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone																										10
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain																										11
RESPIRATORY SYSTEM																										
Larynx																										6
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																				X						2
Alveolar/bronchiolar carcinoma														X			X									2
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver								X									X									4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea																										9
SPECIAL SENSES SYSTEM																										
Harderian gland																							+			1
Bilateral, adenoma																							X			1
URINARY SYSTEM																										
Kidney															+											11
Urinary bladder	+		+	+						+		+					+					+		+	+	27
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed																			X							1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 25 ppm

DAYS ON STUDY	1 4 8	1 4 8	2 5 2	5 7 4	6 6 4	6 8 3	7 0 2	7 0 3	7 1 6	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
CARCASS ID	1 5 3 1	1 5 4 1	1 8 2 1	1 9 1 1	1 9 9 1	1 9 2 1	1 9 5 1	1 9 4 1	1 8 1 1	1 5 9 1	1 6 0 1	1 5 1 1	1 5 2 1	1 5 5 1	1 5 6 1	1 5 7 1	1 5 8 1	1 7 5 1	1 7 1 1	1 7 2 1	1 7 3 1	1 7 4 1	1 8 6 1	1 8 7 1	1 8 8 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	A	M	A	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	M	M	+	+	+	+	+		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Serosa, sarcoma, metastatic, uncertain primary site																									
Intestine large, rectum	M	M	M	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	M	M	M	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	M	M	+	+	A	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X		X														X	
Hepatocellular carcinoma, multiple							X									X									
Hepatocellular adenoma																									X
Sarcoma, metastatic, uncertain primary site																									
Mesentery											+			+											
Fat, hemangiosarcoma																									
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	M	+		+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma, metastatic, uncertain primary site																									
Adrenal gland, cortex	+	+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	M	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	M	M	M	M	+	M	+	+	+	+	M	+	+	M	M	+	+	+	M	+	M	+	+	+	+
Pituitary gland	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X													
Thyroid gland	+		M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS						+																			

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 25 ppm (Continued)

DAYS ON STUDY	733	733	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	TOTAL. TISSUES TUMORS
CARCASS ID	18901	19001	16901	17001	18441	18501	19801	20001	16111	16221	16331	16441	16551	16661	16771	16881	17661	17771	17881	17991	18031	19331	19961	19771	
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	M	M	+	M	+	37
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Serosa, sarcoma, metastatic, uncertain primary site							X																			1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																									X	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma						X		X					X				X									7
Hepatocellular carcinoma, multiple					X		X													X						5
Hepatocellular adenoma																							X			2
Sarcoma, metastatic, uncertain primary site							X																			1
Mesentery															+											3
Fat, hemangiosarcoma															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, uncertain primary site							X																			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Capsule, sarcoma, metastatic, uncertain primary site							X																			1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma								X																		2
Parathyroid gland	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
GENERAL BODY SYSTEM																										
Tissue, NOS																										1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 25 ppm (Continued)

DAYS ON STUDY	148	148	252	574	664	683	702	703	716	731	731	732	732	732	732	732	732	732	733	733	733	733	733	733	733
CARCASS ID	15311	15411	18211	19111	19911	19211	19511	19411	18111	15591	16011	15111	15521	15551	15561	15711	15811	17511	17111	17211	17311	17411	18611	18711	18811
GENITAL SYSTEM																									
Epididymis	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+				+												+						+
Prostate	+	+	M	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, sarcoma, metastatic, uncertain primary site																									
Seminal vesicle	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, sarcoma, metastatic, uncertain primary site																									
Testes	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	M	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	M	+	+
Lymph node, mesenteric	M	M	M	M	+	M	+	+	M			+	M	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma, metastatic, uncertain primary site																									
Thymus		+	M	M	+	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	I	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	M	M	+	+	M	M	M	+	+	+	M	M	M	M	M	M	+	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, hemangioma																								X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lung	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye								+																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	M	+	M	+	+	+	+	+	+	+	-	M	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 25 ppm (Continued)

DAYS ON STUDY	733	733	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	TOTAL:
CARCASS ID	18901	19001	16901	17001	18401	18501	19801	20001	16101	16201	16301	16401	16501	16601	16701	16801	17601	17701	17801	17901	18001	18301	19301	19601	19701	TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+										+	+								+						8
Prostate	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	44
Serosa, sarcoma, metastatic, uncertain primary site							X																			1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Serosa, sarcoma, metastatic, uncertain primary site							X																			1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma												X														1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	M	+	M	35
Lymph node, mesenteric	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	33
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, sarcoma, metastatic, uncertain primary site							X																			1
Thymus	+	+	+	M	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	34
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	M	M	M	M	M	M	M	+	+	+	+	+	M	+	M	M	+	M	+	+	+	21
Skin	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangioma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma													X													2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

	Chamber Control	10 ppm	25 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	(b) 2/23 (9%)	2/48 (4%)
Adjusted Rates (c)	22.9%		4.9%
Terminal Rates (d)	7/33 (21%)		2/41 (5%)
Day of First Observation	588		731
Life Table Test (e)			P=0.023N
Logistic Regression Test (e)			P=0.046N
Fisher Exact Test (e)			P=0.053N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	10/50 (20%)	(b) 12/23 (52%)	12/48 (25%)
Adjusted Rates (c)	23.5%		27.8%
Terminal Rates (d)	4/33 (12%)		10/41 (24%)
Day of First Observation	514		702
Life Table Test (e)			P=0.575
Logistic Regression Test (e)			P=0.363
Fisher Exact Test (e)			P=0.363
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	(b) 14/23 (61%)	14/48 (29%)
Adjusted Rates (c)	41.9%		32.5%
Terminal Rates (d)	11/33 (33%)		12/41 (29%)
Day of First Observation	514		702
Life Table Test (e)			P=0.163N
Logistic Regression Test (e)			P=0.376N
Fisher Exact Test (e)			P=0.384N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	9/50 (18%)	2/49 (4%)	2/49 (4%)
Adjusted Rates (c)	24.8%	6.7%	4.9%
Terminal Rates (d)	6/33 (18%)	2/30 (7%)	2/41 (5%)
Day of First Observation	687	731	731
Life Table Tests (e)	P=0.009N	P=0.043N	P=0.013N
Logistic Regression Tests (e)	P=0.011N	P=0.037N	P=0.018N
Cochran-Armitage Trend Test (e)	P=0.019N		
Fisher Exact Test (e)		P=0.028N	P=0.028N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	0/49 (0%)
Adjusted Rates (c)	8.6%	8.5%	0.0%
Terminal Rates (d)	2/33 (6%)	2/30 (7%)	0/41 (0%)
Day of First Observation	696	358	
Life Table Tests (e)	P=0.072N	P=0.622	P=0.090N
Logistic Regression Tests (e)	P=0.091N	P=0.662N	P=0.111N
Cochran-Armitage Trend Test (e)	P=0.097N		
Fisher Exact Test (e)		P=0.651	P=0.125N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	5/49 (10%)	2/49 (4%)
Adjusted Rates (c)	32.2%	15.1%	4.9%
Terminal Rates (d)	8/33 (24%)	4/30 (13%)	2/41 (5%)
Day of First Observation	687	358	731
Life Table Tests (e)	P=0.001N	P=0.089N	P=0.002N
Logistic Regression Tests (e)	P=0.003N	P=0.065N	P=0.003N
Cochran-Armitage Trend Test (e)	P=0.004N		
Fisher Exact Test (e)		P=0.059N	P=0.004N

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

	Chamber Control	10 ppm	25 ppm
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/49 (6%)	(b) 0/9 (0%)	0/47 (0%)
Adjusted Rates (c)	9.1%		0.0%
Terminal Rates (d)	3/33 (9%)		0/41 (0%)
Day of First Observation	731		
Life Table Test (e)			P=0.086N
Logistic Regression Test (e)			P=0.086N
Fisher Exact Test (e)			P=0.129N
Thyroid Gland: Follicular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	4/49 (8%)	(b) 0/9 (0%)	0/47 (0%)
Adjusted Rates (c)	11.1%		0.0%
Terminal Rates (d)	3/33 (9%)		0/41 (0%)
Day of First Observation	588		
Life Table Test (e)			P=0.046N
Logistic Regression Test (e)			P=0.070N
Fisher Exact Test (e)			P=0.064N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	7/50 (14%)	(b,g) 3/50 (6%)	0/50 (0%)
Adjusted Rates (c)	20.2%	9.1%	0.0%
Terminal Rates (d)	6/33 (18%)	2/30 (7%)	0/41 (0%)
Day of First Observation	670	632	
Life Table Tests (e)	P=0.003N	P=0.203N	P=0.004N
Logistic Regression Tests (e)	P=0.005N	P=0.186N	P=0.006N
Cochran-Armitage Trend Test (e)	P=0.006N		
Fisher Exact Test (e)		P=0.159N	P=0.006N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Fourteen spleens and lymph nodes of 26 animals were examined microscopically.

TABLE C4a. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR NEOPLASMS IN MALE B6C3F$_1$ MICE (a)

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

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Pacific Northwest Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM NEOPLASMS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence for Chamber Controls in NTP Studies (b)		
Propylene oxide	5/50	6/50
Methyl methacrylate	3/50	3/50
Propylene	5/50	5/50
1,2-Epoxybutane	5/49	5/49
Dichloromethane	5/50	5/50
Ethylene oxide	1/50	1/50
Bromoethane	5/50	5/50
Tetrachloroethylene	3/49	3/49
TOTAL	32/398 (8.0%)	33/398 (8.3%)
SD (c)	3.03%	3.29%
Range (d)		
High	5/49	6/50
Low	1/50	1/50
Overall Historical Incidence for Untreated Controls in NTP Studies		
TOTAL	193/1,692 (11.4%)	196/1,692 (11.6%)
SD (c)	6.07%	6.31%
Range (d)		
High	13/50	14/50
Low	1/50	1/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) All studies were conducted at Battelle Pacific Northwest Laboratories.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

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

	Chamber Control	10 ppm	25 ppm
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(9)	(48)
Inflammation, chronic active	1 (2%)	1 (11%)	
Gallbladder	(41)	(10)	(37)
Epithelium, hyperplasia	1 (2%)		
Intestine large, cecum	(46)	(7)	(44)
Hyperplasia, lymphoid, focal			1 (2%)
Mucosa, necrosis, acute			1 (2%)
Liver	(50)	(23)	(48)
Angiectasis, multifocal			1 (2%)
Anisokaryosis	1 (2%)		
Basophilic focus	2 (4%)		
Basophilic focus, multiple			1 (2%)
Cyst multilocular	2 (4%)		1 (2%)
Cytomegaly, focal			1 (2%)
Degeneration, ballooning, multifocal			1 (2%)
Fatty change, focal	1 (2%)		1 (2%)
Fibrosis, focal			1 (2%)
Hematopoietic cell proliferation, multifocal	1 (2%)	1 (4%)	
Hepatodiaphragmatic nodule			1 (2%)
Infarct, single	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Infiltration cellular, histiocytic, multifocal	1 (2%)		
Inflammation, acute, multifocal	1 (2%)		
Karyomegaly, multifocal	1 (2%)		
Necrosis, acute, focal		3 (13%)	1 (2%)
Necrosis, acute, multifocal	2 (4%)	2 (9%)	2 (4%)
Necrosis, subacute, multifocal	1 (2%)		
Syncytial alteration, focal			1 (2%)
Syncytial alteration, multifocal	1 (2%)		
Median lobe, congestion, diffuse	1 (2%)		
Median lobe, fibrosis	1 (2%)		
Median lobe, thrombus	1 (2%)		
Median lobe, hepatocyte, atrophy, diffuse	1 (2%)		
Mesentery	(6)		(3)
Infiltration cellular, lymphocytic, multifocal	2 (33%)		1 (33%)
Inflammation, acute, focal	1 (17%)		
Artery, adventitia, infiltration cellular, mixed cell, focal	1 (17%)		
Fat, inflammation, chronic active, focal			1 (33%)
Pancreas	(49)	(9)	(49)
Infiltration cellular, lymphocytic, multifocal	1 (2%)		2 (4%)
Acinus, atrophy, multifocal	1 (2%)		
Acinus, hyperplasia, focal	1 (2%)		
Acinus, hypertrophy, focal			1 (2%)
Acinus, hypertrophy, multifocal	1 (2%)		
Artery, inflammation, chronic active, focal	1 (2%)		
Salivary glands	(50)	(11)	(50)
Infiltration cellular, lymphocytic, focal			1 (2%)
Infiltration cellular, lymphocytic, multifocal	24 (48%)	2 (18%)	24 (48%)
Stomach, forestomach	(48)	(10)	(47)
Hyperplasia, squamous, focal	1 (2%)		
Epithelium, hyperplasia, focal	1 (2%)		1 (2%)
Stomach, glandular	(47)	(11)	(49)
Inflammation, chronic active, focal			1 (2%)
Inflammation, chronic active, multifocal			1 (2%)

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

	Chamber Control	10 ppm	25 ppm
CARDIOVASCULAR SYSTEM			
Heart	(50)	(13)	(50)
Cardiomyopathy		1 (8%)	1 (2%)
Artery, embolus, single	1 (2%)		
Artery, inflammation, chronic active		1 (8%)	
Coronary artery, infiltration cellular, mixed cell, focal	1 (2%)		
Mitral valve, pigmentation, hemosiderin, focal	1 (2%)		
Myocardium, inflammation, chronic active, multifocal	1 (2%)		
Perivascular, inflammation, acute, focal	1 (2%)		
Ventricle, karyomegaly, multifocal	1 (2%)		
Ventricle left, bacterium	1 (2%)		
Ventricle left, inflammation, subacute, focal	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(49)	(10)	(48)
Accessory adrenal cortical nodule	1 (2%)		3 (6%)
Capsule, hyperplasia, focal	3 (6%)		2 (4%)
Capsule, hyperplasia, multifocal	36 (73%)	3 (30%)	39 (81%)
Adrenal gland, cortex	(49)	(10)	(48)
Hyperplasia, focal	5 (10%)		7 (15%)
Hyperplasia, multifocal	6 (12%)		5 (10%)
Hypertrophy, focal	7 (14%)	1 (10%)	8 (17%)
Hypertrophy, multifocal	6 (12%)		3 (6%)
Adrenal gland, medulla	(49)	(9)	(47)
Hyperplasia, focal	1 (2%)		
Islets, pancreatic	(49)	(9)	(49)
Hyperplasia, focal			2 (4%)
Hyperplasia, multifocal	7 (14%)	1 (11%)	4 (8%)
Parathyroid gland	(36)	(6)	(35)
Infiltration cellular, lymphocytic, focal			1 (3%)
Pituitary gland	(45)	(11)	(47)
Pars distalis, cyst	2 (4%)		2 (4%)
Thyroid gland	(49)	(9)	(47)
Infiltration cellular, lymphocytic, focal			1 (2%)
Inflammation, chronic, focal			1 (2%)
Ultimobranchial cyst	1 (2%)		2 (4%)
Follicular cell, hyperplasia	1 (2%)		
Follicular cell, hyperplasia, multifocal	1 (2%)		
GENERAL BODY SYSTEM			
Tissue, NOS		(1)	(1)
Inflammation, chronic active, multifocal		1 (100%)	
GENITAL SYSTEM			
Coagulating gland	(1)		
Inflammation, chronic active	1 (100%)		
Preputial gland	(15)	(6)	(8)
Abscess	6 (40%)	1 (17%)	
Cyst	5 (33%)	1 (17%)	8 (100%)
Cyst multilocular	1 (7%)		
Dilatation		1 (17%)	
Inflammation, chronic	3 (20%)	3 (50%)	
Inflammation, chronic active	7 (47%)		
Prostate	(46)	(9)	(44)
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Inflammation, chronic active	3 (7%)	1 (11%)	
Inflammation, suppurative, acute	1 (2%)		

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

	Chamber Control	10 ppm	25 ppm
GENITAL SYSTEM (Continued)			
Seminal vesicle	(48)	(17)	(49)
Dilatation	1 (2%)	1 (6%)	
Testes	(50)	(12)	(49)
Left, hemorrhage			1 (2%)
Seminiferous tubule, atrophy	3 (6%)	1 (8%)	3 (6%)
Seminiferous tubule, degeneration, multifocal	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(49)	(10)	(49)
Myeloid cell, hyperplasia	5 (10%)	2 (20%)	
Lymph node	(50)	(26)	(50)
Angiectasis, focal		1 (4%)	
Bronchial, hemorrhage			1 (2%)
Inguinal, hyperplasia, lymphoid		1 (4%)	
Inguinal, hyperplasia, re cell	1 (2%)		
Lumbar, hemorrhage	1 (2%)		
Lumbar, hyperplasia, lymphoid	1 (2%)		
Mediastinal, hyperplasia, lymphoid		1 (4%)	1 (2%)
Lymph node, mandibular	(47)	(11)	(35)
Hyperplasia, lymphoid			2 (6%)
Hyperplasia, re cell	3 (6%)		3 (9%)
Lymph node, mesenteric	(42)	(19)	(33)
Hematopoietic cell proliferation	6 (14%)	4 (21%)	
Hemorrhage	25 (60%)	12 (63%)	14 (42%)
Hyperplasia		1 (5%)	
Hyperplasia, lymphoid		1 (5%)	2 (6%)
Hyperplasia, re cell	2 (5%)		3 (9%)
Spleen	(49)	(14)	(49)
Angiectasis, multifocal			1 (2%)
Depletion lymphoid	1 (2%)		
Hematopoietic cell proliferation	11 (22%)	6 (43%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
Hyperplasia, lymphoid, diffuse			1 (2%)
Hyperplasia, plasma cell			1 (2%)
Hyperplasia, re cell	1 (2%)		
Thrombus			1 (2%)
Lymphocyte, necrosis, multifocal			1 (2%)
Thymus	(35)	(6)	(34)
Cyst, multiple			1 (3%)
Depletion lymphoid	1 (3%)	1 (17%)	1 (3%)
Hyperplasia, lymphoid, diffuse			1 (3%)
Inflammation, acute		1 (17%)	
Syncytial alteration	1 (3%)		
INTEGUMENTARY SYSTEM			
Skin	(50)	(30)	(49)
Inflammation, chronic active	1 (2%)	1 (3%)	1 (2%)
Ulcer		1 (3%)	
Prepuce, abscess		2 (7%)	
Prepuce, inflammation, chronic active		1 (3%)	
Prepuce, necrosis	3 (6%)		
Prepuce, ulcer	2 (4%)	2 (7%)	
Scrotal, pigmentation, melanin, focal		1 (3%)	
Scrotal, hair follicle, hyperplasia, focal		1 (3%)	
Subcutaneous tissue, abscess		1 (3%)	
Subcutaneous tissue, cyst	1 (2%)		
Subcutaneous tissue, edema		1 (3%)	
Subcutaneous tissue, inflammation, granulomatous, focal	1 (2%)		

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

	Chamber Control	10 ppm	25 ppm
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(10)	(50)
Hyperostosis	1 (2%)		
Osteoporosis, focal			1 (2%)
Sternum, developmental malformation	1 (2%)		
Skeletal muscle		(1)	(1)
Arteriole, inflammation, chronic active		1 (100%)	
NERVOUS SYSTEM			
Brain	(50)	(11)	(50)
Hydrocephalus	1 (2%)		
Mineralization, focal	1 (2%)		
Mineralization, multifocal	26 (52%)	5 (45%)	21 (42%)
Artery, meninges, inflammation, chronic, multifocal			1 (2%)
RESPIRATORY SYSTEM			
Larynx	(44)	(6)	(46)
Inflammation, acute, diffuse			1 (2%)
Inflammation, chronic, focal	1 (2%)		
Inflammation, chronic, multifocal			1 (2%)
Lung	(50)	(49)	(49)
Congestion		1 (2%)	1 (2%)
Granuloma			1 (2%)
Infiltration cellular, lymphocytic, multifocal	5 (10%)	1 (2%)	3 (6%)
Infiltration cellular, histiocytic, diffuse	1 (2%)		
Infiltration cellular, histiocytic, focal		2 (4%)	1 (2%)
Infiltration cellular, histiocytic, multifocal		3 (6%)	1 (2%)
Alveolar epithelium, hyperplasia, focal	2 (4%)	2 (4%)	
Alveolus, infiltration cellular, histiocytic, multifocal			1 (2%)
Alveolus, inflammation, chronic active, focal		1 (2%)	1 (2%)
Alveolus, inflammation, chronic active, multifocal			3 (6%)
Bronchiole, hyperplasia, focal		1 (2%)	
Bronchiole, hyperplasia, multifocal		4 (8%)	
Bronchiole, inflammation, chronic, focal		1 (2%)	
Bronchiole, alveolus, inflammation, chronic, multifocal		1 (2%)	
Bronchiole, alveolus, inflammation, chronic active, focal		3 (6%)	1 (2%)
Bronchiole, alveolus, inflammation, chronic active, multifocal		12 (24%)	29 (59%)
Interstitium, inflammation, acute, focal	1 (2%)		
Mediastinum, infiltration cellular, lymphocytic, multifocal		1 (2%)	2 (4%)
Pleura, hyperplasia, diffuse			1 (2%)
Pleura, infiltration cellular, lymphocytic		1 (2%)	
Nose	(50)	(48)	(49)
Mucosa, inflammation, acute	3 (6%)		1 (2%)
Mucosa, inflammation, chronic	1 (2%)		
Mucosa, inflammation, chronic active	2 (4%)	47 (98%)	48 (98%)
Nasolacrimal duct, inflammation, chronic	1 (2%)		
Nasolacrimal duct, inflammation, chronic active		1 (2%)	
Respiratory epithelium, hyperplasia	5 (10%)	48 (100%)	49 (100%)
Trachea	(49)	(9)	(48)
Inflammation, chronic, focal			1 (2%)
Glands, hyperplasia, diffuse			2 (4%)

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

	Chamber Control	10 ppm	25 ppm
SPECIAL SENSES SYSTEM			
Eye			(1)
Left, cornea, inflammation, chronic active			1 (100%)
URINARY SYSTEM			
Kidney	(49)	(11)	(50)
Congestion			1 (2%)
Cyst, single	1 (2%)		
Degeneration, chronic, focal, two			1 (2%)
Degeneration, chronic, multifocal			1 (2%)
Embolus, multifocal	1 (2%)		
Hydronephrosis	3 (6%)		1 (2%)
Infiltration cellular, lymphocytic, focal	1 (2%)		1 (2%)
Infiltration cellular, lymphocytic, multifocal	9 (18%)		3 (6%)
Infiltration cellular, mixed cell, multifocal	1 (2%)		
Inflammation, acute, focal		1 (9%)	
Inflammation, suppurative, acute, multifocal	1 (2%)		
Inflammation, suppurative, chronic active, multifocal	2 (4%)	1 (9%)	
Mineralization, focal	1 (2%)		
Mineralization, multifocal		1 (9%)	
Nephropathy, chronic		1 (9%)	3 (6%)
Artery, inflammation			1 (2%)
Capsule, fibrosis, multifocal		1 (9%)	
Cortex, renal tubule, epithelium, hyperplasia, atypical, focal	1 (2%)		
Urethra	(1)		
Calculus micro observation only	1 (100%)		
Urinary bladder	(49)	(27)	(47)
Calculus micro observation only	2 (4%)		
Embolus	1 (2%)		
Inflammation, chronic active, diffuse	1 (2%)	1 (4%)	
Inflammation, chronic active, multifocal	1 (2%)		

APPENDIX D

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

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

	Chamber Control	10 ppm	25 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund sacrifice	6	10	1
Natural death	8	2	7
Accidentally killed		1	2
Dosing accident			6
Survivors			
Terminal sacrifice	36	37	34
Animals examined microscopically	48	49	50
ALIMENTARY SYSTEM			
Esophagus	(48)	(1)	(47)
Gallbladder	(38)	(2)	(42)
Intestine large, colon	(47)	(2)	(46)
Intestine large, rectum	(47)	(1)	(40)
Intestine small	(46)	(6)	(47)
Intestine small, duodenum	(45)	(3)	(44)
Polyp adenomatous		1 (33%)	
Liver	(48)	(16)	(49)
Hemangiosarcoma		1 (6%)	
Hemangiosarcoma, metastatic, spleen		1 (6%)	
Hepatocellular carcinoma	6 (13%)	2 (13%)	
Hepatocellular carcinoma, multiple		1 (6%)	
Hepatocellular adenoma	4 (8%)	2 (13%)	2 (4%)
Mesentery	(8)	(3)	(2)
Plasma cell tumor malignant			1 (50%)
Pancreas	(47)	(3)	(49)
Salivary glands	(48)	(1)	(48)
Plasma cell tumor malignant			1 (2%)
Stomach, forestomach	(47)	(3)	(45)
Stomach, glandular	(47)	(3)	(47)
Hamartoma	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(48)	(2)	(48)
ENDOCRINE SYSTEM			
Adrenal gland	(47)	(3)	(49)
Adrenal gland, medulla	(45)	(2)	(47)
Pheochromocytoma benign	1 (2%)		
Islets, pancreatic	(47)	(3)	(49)
Carcinoma		1 (33%)	
Parathyroid gland	(29)	(1)	(25)
Pituitary gland	(46)	(5)	(47)
Pars distalis, adenoma	8 (17%)	3 (60%)	2 (4%)
Pars intermedia, adenoma	1 (2%)		1 (2%)
Thyroid gland	(48)	(2)	(42)
Follicular cell, adenoma	1 (2%)		
GENERAL BODY SYSTEM			
None			

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

	Chamber Control	10 ppm	25 ppm
GENITAL SYSTEM			
Ovary	(46)	(14)	(44)
Adenoma		1 (7%)	
Granulosa cell tumor malignant	1 (2%)		
Hemangioma	1 (2%)		
Plasma cell tumor malignant			1 (2%)
Uterus	(48)	(37)	(45)
Granulosa cell tumor malignant, metastatic, uterus	1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (3%)	
Plasma cell tumor malignant			1 (2%)
Polyp stromal	2 (4%)	1 (3%)	
Sarcoma stromal		1 (3%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(47)	(2)	(47)
Lymph node	(48)	(8)	(49)
Lymph node, mandibular	(45)	(1)	(43)
Plasma cell tumor malignant			1 (2%)
Lymph node, mesenteric	(38)	(6)	(32)
Spleen	(47)	(13)	(49)
Hemangiosarcoma		3 (23%)	
Thymus	(40)	(2)	(42)
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(1)	(44)
Adenocarcinoma	2 (4%)		
Skin	(46)	(20)	(47)
Subcutaneous tissue, fibrosarcoma		2 (10%)	
Subcutaneous tissue, hemangioma		1 (5%)	
Subcutaneous tissue, sarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Larynx	(40)	(1)	(40)
Plasma cell tumor malignant			1 (3%)
Lung	(48)	(49)	(49)
Adenocarcinoma, metastatic, mammary gland	1 (2%)		
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		2 (4%)
Hepatocellular carcinoma, metastatic		1 (2%)	
Pleura, mediastinum, plasma cell tumor malignant			1 (2%)
Trachea	(48)	(2)	(47)
Plasma cell tumor malignant			1 (2%)
SPECIAL SENSES SYSTEM			
Harderian gland	(1)		(1)
Adenoma, papillary	1 (100%)		
Carcinoma			1 (100%)
Lacrimal gland	(10)		(5)

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

	Chamber Control	10 ppm	25 ppm
URINARY SYSTEM			
Kidney	(48)	(7)	(49)
Hemangiosarcoma, metastatic, spleen		1 (14%)	
Urinary bladder	(45)	(2)	(40)
SYSTEMIC LESIONS			
Multiple organs	*(48)	*(49)	*(50)
Lymphoma malignant histiocytic	3 (6%)	2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	7 (15%)		4 (8%)
Lymphoma malignant mixed	4 (8%)	5 (10%)	1 (2%)
Lymphoma malignant undifferentiated cell	2 (4%)	2 (4%)	1 (2%)
TUMOR SUMMARY			
Total animals with primary neoplasms **	29	27	17
Total primary neoplasms	48	31	27
Total animals with benign neoplasms	16	11	7
Total benign neoplasms	22	11	7
Total animals with malignant neoplasms	22	18	12
Total malignant neoplasms	26	20	20
Total animals with secondary neoplasms ***	2	2	
Total secondary neoplasms	2	4	

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

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

DAYS ON STUDY	0 4 7	4 6 9	5 6 0	5 7 4	5 8 9	6 7 2	6 9 2	6 9 2	7 0 0	7 0 5	7 0 9	7 1 4	7 1 5	7 2 8	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
CARCASS ID	2 2 1	1 9 1	3 1 1	4 8 1	0 7 1	4 5 1	1 4 1	1 8 1	4 6 1	2 1 1	2 3 1	1 3 1	0 4 1	0 9 1	1 2 1	2 9 1	1 0 1	1 1 1	1 5 1	2 5 1	2 6 1	2 7 1	2 8 1	3 0 1	4 1 1
ALIMENTARY SYSTEM																									
Esophagus		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder		+	+	+	A	+		+	M	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large		+	+	+	A	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum		M	+	+		+		+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon		+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum		+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small		+	+	+	A	+		+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum		+	+	+		+		+	+	+		+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum			+	+		+		+	+	+		+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum			+	+		+		+	+	+		+	+	+	+	A		+	+	+	+	+	+	+	+
Liver		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X					X			X	X								X
Hepatocellular adenoma								X																	
Mesentery						+			+		+		+		+				+						
Pancreas		+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																									
Salivary glands		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach		+	+	+	A	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hamartoma																									
Tooth																						+			
CARDIOVASCULAR SYSTEM																									
Heart		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla			+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic		+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland		+	M	+	M	+		M	+	+	M	+	+	M	M	+	+	M	M	M	+	+	+	+	M
Pituitary gland		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma									X	X													X		X
Pars intermedia, adenoma																									
Thyroid gland		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

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

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

DAYS ON STUDY	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	TOTAL.
CARCASS ID	4 2 1	4 3 1	4 4 1	0 5 1	0 6 1	0 8 1	2 4 1	3 6 1	3 7 1	3 8 1	3 9 1	4 0 1	2 0 1	3 4 1	3 5 1	4 9 1	5 0 1	0 1 1	0 2 1	0 3 1	1 6 1	1 7 1	3 2 1	3 3 1	4 7 1	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	M	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	A	+	+	+	+	M	38
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma																						X				6
Hepatocellular adenoma								X	X							X										4
Mesentery										+												+				8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pharynx																									+	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	47
Hamartoma																							X			1
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	47
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	45
Pheochromocytoma benign										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	M	M	+	+	M	M	+	M	+	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Pars distalis, adenoma		X							X				X			X										8
Pars intermedia, adenoma	X																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma																							X			1
GENERAL BODY SYSTEM																										
None																										

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

DAYS ON STUDY	047	469	560	574	589	672	692	692	700	705	709	714	715	728	731	731	732	732	732	732	732	732	732	732	732
CARCASS ID	221	191	311	481	071	451	141	181	461	211	231	131	041	091	121	291	101	111	151	251	261	271	281	301	411
GENITAL SYSTEM																									
Clitoral gland																									
Ovary		+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Hemangioma																		X							
Uterus		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, uterus																									
Polyp stromal																									
HEMATOPOIETIC SYSTEM																									
Bone marrow		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular		+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Lymph node, mesenteric		+	M	+	M	M		+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen		+	+	+	A	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus		M	M	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx			+	+	+	+		+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma												X													
Nose		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																									
Adenoma, papillary																									
Lacrimal gland									+								+	+							
URINARY SYSTEM																									
Kidney		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder		+	+	M	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs		+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X				X			X												
Lymphoma malignant lymphocytic											X						X					X			
Lymphoma malignant mixed								X						X											
Lymphoma malignant undifferentiated cell type									X																

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

DAYS ON STUDY	732	732	732	733	733	733	733	733	733	733	733	733	734	734	734	734	735	735	735	735	735	735	735	735	TOTAL
CARCASS ID	4211	4311	4411	0511	0611	0811	2411	3611	3711	3811	3911	4011	2011	3411	3511	4911	5011	0111	0211	0311	1611	1711	3211	3311	4711	TISSUES TUMORS
GENITAL SYSTEM																										
Clitoral gland																							+			1
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Granulosa cell tumor malignant							X																			1
Hemangioma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor malignant, metastatic, uterus							X																			1
Polyp stromal										X													X			2
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	M	+	I	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	M	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	40
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Adenocarcinoma																							X		X	2
Skin	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	M	+	40
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, metastatic, mammary gland																									X	1
Alveolar/bronchiolar adenoma																X					X					2
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye			+		+																					2
Harderian gland			+																							1
Adenoma, papillary			X																							1
Lacrimal gland	+						+									+				+	+	+			+	10
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										3
Lymphoma malignant lymphocytic	X		X					X		X																7
Lymphoma malignant mixed																				X		X				4
Lymphoma malignant undifferentiated cell type															X											2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 10 ppm

DAYS ON STUDY	4 5 9	5 8 2	6 0 6	6 5 7	6 6 5	6 7 9	6 7 9	6 9 0	6 9 3	6 9 6	6 9 6	7 1 4	7 1 4	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3
CARCASS ID	2 4 9 1	2 1 7 1	2 2 3 1	2 3 5 1	2 0 9 1	2 0 7 1	2 1 5 1	2 1 8 1	2 1 0 1	2 2 6 1	2 3 7 1	2 2 5 1	2 3 9 1	2 3 0 1	2 4 5 1	2 1 2 1	2 1 3 1	2 1 4 1	2 2 8 1	2 2 9 1	2 4 3 1	2 4 4 1	2 0 8 1	2 1 1 1	2 2 2 1
ALIMENTARY SYSTEM																									
Esophagus	M	+																							
Gallbladder	+																								
Intestine large	+	+																							
Intestine large, cecum	+	+																							
Intestine large, colon	+	+																							
Intestine large, rectum	M	+																							
Intestine small	+	+													+										+
Intestine small, duodenum	+	+																							+
Polyp adenomatous																									X
Intestine small, ileum	+	+																							
Intestine small, jejunum	A	+																							
Liver	+	+		+	+		+		+	+	+	+		+									+		+
Hemangiosarcoma																									X
Hemangiosarcoma, metastatic, spleen				X																					
Hepatocellular carcinoma											X														
Hepatocellular carcinoma, multiple							X																		
Hepatocellular adenoma																							X		
Mesentery										+						+									
Pancreas	+	+																							
Salivary glands	+	M																							
Stomach	+	+																							
Stomach, forestomach	+	+																							
Stomach, glandular	+	+																							
CARDIOVASCULAR SYSTEM																									
Heart	+	+																							
ENDOCRINE SYSTEM																									
Adrenal gland	+	+											+												
Extra adrenal tissue, lymphoma																									
Adrenal gland, cortex	+	M											+												
Adrenal gland, medulla	+	M											+												
Islets, pancreatic	+	+																							
Carcinoma																									
Parathyroid gland	M	+																							
Pituitary gland	+	+																	+						
Pars distalis, adenoma																			X						
Thyroid gland	+	+																							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+		+							+					+		+							+
Adenoma																									
Uterus	+	+		+			+			+		+		+	+	+	+	+		+	+	+	+		+
Hemangiosarcoma, metastatic, spleen				X																					
Polyp stromal																	X								
Sarcoma stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 ppm (Continued)

DAYS ON STUDY	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	TOTAL:
CARCASS ID	2 2 4 1	2 2 7 1	2 3 8 1	2 4 0 1	2 4 1 1	2 4 2 1	2 0 2 1	2 0 6 1	2 2 0 1	2 2 1 1	2 3 6 1	2 5 0 1	2 0 1 1	2 0 3 1	2 0 4 1	2 0 5 1	2 1 6 1	2 1 9 1	2 3 1 1	2 3 2 1	2 3 3 1	2 3 4 1	2 4 6 1	2 4 7 1	2 4 8 1	TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus																										1
Gallbladder				+																						2
Intestine large																										2
Intestine large, cecum																										2
Intestine large, colon																										2
Intestine large, rectum																										1
Intestine small					+													+								6
Intestine small, duodenum																										3
Polyp adenomatous																										1
Intestine small, ileum																										2
Intestine small, jejunum																										1
Liver				+													+				+	+				16
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma																						X				2
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma																	X									2
Mesentery																	+									3
Pancreas				+																						3
Salivary glands																										1
Stomach																	+									3
Stomach, forestomach																	+									3
Stomach, glandular																	+									3
CARDIOVASCULAR SYSTEM																										
Heart																										2
ENDOCRINE SYSTEM																										
Adrenal gland																										3
Extra adrenal tissue, lymphoma																										
Adrenal gland, cortex																										2
Adrenal gland, medulla																										2
Islets, pancreatic				+																						3
Carcinoma				X																						1
Parathyroid gland																										1
Pituitary gland														+					+							5
Pars distalis, adenoma														X					X							3
Thyroid gland																										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary		+				+		+			+	+	+						+							14
Adenoma								X																		1
Uterus	+	+	+	+	+		+	+	+			+	+	+	+	+	+	+		+	+	+	+	+	+	37
Hemangiosarcoma, metastatic, spleen																										1
Polyp stromal																										1
Sarcoma stromal																							X			1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 ppm (Continued)

DAYS ON STUDY	459	582	606	657	665	679	679	690	693	696	696	714	714	731	731	732	732	732	732	732	732	732	733	733	733
CARCASS ID	24901	21711	22331	23551	20901	20711	21511	21811	21011	22611	23711	22511	23901	23001	24511	21211	21311	21411	22811	22291	24311	24411	20811	21111	22211
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+																							
Lymph node	+	+		+	+						+		+		+										
Lymph node, mandibular	+	M																							
Lymph node, mesenteric	M	+		+	+						+		+		+										
Spleen	+	+		+	+		+		+	+	+	+	+	+											
Hemangiosarcoma				X			X							X											
Thymus	+	M			+																				
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+																							
Skin	+	+			+	+	+		+	+				+			+				+		+	+	
Subcutaneous tissue, fibrosarcoma						X				X															
Subcutaneous tissue, hemangioma		X																							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+													+					+	+				
NERVOUS SYSTEM																									
Brain	+	+																							
RESPIRATORY SYSTEM																									
Larynx	M	+																							
Lung	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Hepatocellular carcinoma, metastatic																									
Nose	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+																							
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+		+	+				+																+
Hemangiosarcoma, metastatic, spleen				X																					
Urinary bladder	+	+																							
SYSTEMIC LESIONS																									
Multiple organs	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic									X			X													
Lymphoma malignant mixed					X						X														
Lymphoma malignant undifferentiated cell type													X												

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 ppm (Continued)

DAYS ON STUDY	733	733	733	733	733	733	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	735	735	TOTAL.
CARCASS ID	22441	22711	23811	24401	24411	24211	20201	20661	22201	22111	23631	25011	20111	20031	20411	20511	21611	21911	23111	23211	23311	23411	24611	24711	24811	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow																										2
Lymph node											+															8
Lymph node, mandibular																										1
Lymph node, mesenteric																										6
Spleen					+													+								13
Hemangiosarcoma																										3
Thymus																										2
INTEGUMENTARY SYSTEM																										
Mammary gland																										1
Skin		+	+			+	+						+					+	+			+				20
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, hemangioma																										1
MUSCULOSKELETAL SYSTEM																										
Bone				+	+		+	+			+											+		+		12
NERVOUS SYSTEM																										
Brain																										2
RESPIRATORY SYSTEM																										
Larynx																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X															X								2
Hepatocellular carcinoma, metastatic																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea																										2
SPECIAL SENSES SYSTEM																										
None																										
URINARY SYSTEM																										
Kidney																					+					7
Hemangiosarcoma, metastatic, spleen																										1
Urinary bladder																										2
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed					X													X			X					5
Lymphoma malignant undifferentiated cell type											X															2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF VINYL TOLUENE: 25 ppm

DAYS ON STUDY	003	042	148	148	148	148	148	148	350	464	603	616	667	672	674	728	731	731	732	732	732	732	732	732	732
CARCASS ID	110 01	120 21	122 31	123 41	124 41	137 11	138 11	139 11	134 11	105 11	119 11	113 11	102 11	140 11	132 11	118 11	115 11	130 11	112 11	114 11	128 11	129 11	143 11	144 11	145 11
ALIMENTARY SYSTEM																									
Esophagus	+	M	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	M	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum			+	+	M	M	M	+		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon			+	+	+	+	+	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum			M	M	M	M	M	M		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	M	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum			+	+	+	+	+	M		A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum			M	M	M	M	M	M		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum			M	M	M	M	M	M		A	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+
Liver	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X																							
Mesentery															+	+									
Plasma cell tumor malignant																X									
Pancreas	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																X									
Stomach	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	M	+	M	M	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	M	+	+	+	+	+	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	A	+		+		+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	A	+		+		+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	M	M	M	M	M		+	+	+	M	M	M	+	+	M	M	M	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	M	+	M	M	+	+	M	M		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Clitoral gland																									
Ovary	M	M	+	+	M	+	+	+		+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Plasma cell tumor malignant																X									
Uterus	+	M	+	M	+	M	+	+		+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																X									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 ppm (Continued)

DAYS ON STUDY	733	733	733	733	733	733	733	733	733	734	734	734	734	734	735	735	735	735	735	735	735	735	735	735	TOTAL: TISSUES TUMORS
CARCASS ID	10701	10801	10901	11101	12501	12601	12701	14101	14201	10401	10601	12101	13301	13501	13601	10101	10301	11601	11701	13101	14601	14701	14801	14901	15001	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X																								2
Mesentery																										2
Plasma cell tumor malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Plasma cell tumor malignant																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth											+															1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	+	M	M	+	M	+	+	M	+	+	+	+	M	+	+	+	M	M	+	+	M	+	+	25
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma						X																	X			2
Pars intermedia, adenoma																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	42
GENERAL BODY SYSTEM																										
Tissue, NOS					+																					1
GENITAL SYSTEM																										
Clitoral gland															+											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Plasma cell tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Plasma cell tumor malignant																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 ppm (Continued)

DAYS ON STUDY	003	042	148	148	148	148	148	148	350	464	603	616	667	672	674	728	731	731	732	732	732	732	732	732	732
CARCASS ID	11001	12001	12201	12301	12401	13701	13801	13901	13401	10501	11901	11301	10201	14001	13201	11801	11501	13001	11211	11141	12881	12291	14431	14441	14551
HEMATOPOIETIC SYSTEM																									
Bone marrow	M	M	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	M	+	+	M	M	+	+		M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																X									
Lymph node, mesenteric		M	M	M	M	M	M	M		+	+	M	+	M	+	M	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	M	+	+	+	+	+	+	A	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	+	M	M	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	M	+	+		+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Subcutaneous tissue, sarcoma																				X					
MUSCULOSKELETAL SYSTEM																									
Bone	M	M	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	M	+	+	M	M	M	M	M		M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Plasma cell tumor malignant																X									
Lung	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma										X															
Pleura, mediastinum, plasma cell tumor malignant																X									
Nose	+	I	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant																X									
SPECIAL SENSES SYSTEM																									
Harderian gland																						+			
Carcinoma																						X			
Lacrimal gland																				+					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	M	M	M	M	M	M	M	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																						X		X	
Lymphoma malignant lymphocytic														X	X										
Lymphoma malignant mixed											X														
Lymphoma malignant undifferentiated cell type													X												

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 25 ppm (Continued)

DAYS ON STUDY	733	733	733	733	733	733	733	733	733	734	734	734	734	734	734	735	735	735	735	735	735	735	735	735	TOTAL TISSUES TUMORS
CARCASS ID	10701	10801	10901	11101	12251	12261	12271	14111	14211	10401	10601	12111	13131	13351	13361	10111	10131	11161	11171	13111	14461	14471	14481	14491	15001	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Plasma cell tumor malignant																										1
Lymph node, mesenteric	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	32
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Plasma cell tumor malignant																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma											X															2
Alveolar/bronchiolar carcinoma	X																									2
Pleura, mediastinum, plasma cell tumor malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Plasma cell tumor malignant																										1
SPECIAL SENSES SYSTEM																										
Harderian gland																										1
Carcinoma																										1
Lacrimal gland					+	+								+									+			5
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant histiocytic																										2
Lymphoma malignant lymphocytic						X								X												4
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1

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

	Chamber Control	10 ppm	25 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/48 (8%)	(b) 2/16 (13%)	2/49 (4%)
Adjusted Rates (c)	10.5%		4.9%
Terminal Rates (d)	3/36 (8%)		1/34 (3%)
Day of First Observation	692		42
Life Table Test (e)			P=0.371N
Logistic Regression Test (e)			P=0.233N
Fisher Exact Test (e)			P=0.329N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/48 (13%)	(b) 3/16 (19%)	0/49 (0%)
Adjusted Rates (c)	15.5%		0.0%
Terminal Rates (d)	4/36 (11%)		0/34 (0%)
Day of First Observation	692		
Life Table Test (e)			P=0.025N
Logistic Regression Test (e)			P=0.026N
Fisher Exact Test (e)			P=0.012N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	9/48 (19%)	(b) 5/16 (31%)	2/49 (4%)
Adjusted Rates (c)	23.4%		4.9%
Terminal Rates (d)	7/36 (19%)		1/34 (3%)
Day of First Observation	692		42
Life Table Test (e)			P=0.039N
Logistic Regression Test (e)			P=0.021N
Fisher Exact Test (e)			P=0.023N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	2/49 (4%)	4/49 (8%)
Adjusted Rates (c)	8.0%	5.4%	11.0%
Terminal Rates (d)	2/36 (6%)	2/37 (5%)	3/34 (9%)
Day of First Observation	714	731	464
Life Table Tests (e)	P=0.362	P=0.490N	P=0.458
Logistic Regression Tests (e)	P=0.363	P=0.495N	P=0.464
Cochran-Armitage Trend Test (e)	P=0.410		
Fisher Exact Test (e)		P=0.490N	P=0.512
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	8/46 (17%)	(b) 3/5 (60%)	2/47 (4%)
Adjusted Rates (c)	21.6%		6.1%
Terminal Rates (d)	6/34 (18%)		2/33 (6%)
Day of First Observation	700		731
Life Table Test (e)			P=0.060N
Logistic Regression Test (e)			P=0.068N
Fisher Exact Test (e)			P=0.042N
Circulatory System: Hemangiosarcoma			
Overall Rates (f)	0/48 (0%)	4/49 (8%)	0/50 (0%)
Adjusted Rates (c)	0.0%	9.5%	0.0%
Terminal Rates (d)	0/36 (0%)	2/37 (5%)	0/34 (0%)
Day of First Observation		657	
Life Table Tests (e)	P=0.558N	P=0.072	(g)
Logistic Regression Tests (e)	P=0.538N	P=0.063	(g)
Cochran-Armitage Trend Test (e)	P=0.503N		
Fisher Exact Test (e)		P=0.061	(g)

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

	Chamber Control	10 ppm	25 ppm
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (f)	1/48 (2%)	5/49 (10%)	0/50 (0%)
Adjusted Rates (c)	2.8%	11.4%	0.0%
Terminal Rates (d)	1/36 (3%)	2/37 (5%)	0/34 (0%)
Day of First Observation	731	582	
Life Table Tests (e)	P=0.348N	P=0.119	P=0.511N
Logistic Regression Tests (e)	P=0.297N	P=0.098	P=0.511N
Cochran-Armitage Trend Test (e)	P=0.292N		
Fisher Exact Test (e)		P=0.107	P=0.490N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	16/48 (33%)	9/49 (18%)	8/50 (16%)
Adjusted Rates (c)	37.0%	21.2%	20.8%
Terminal Rates (d)	9/36 (25%)	4/37 (11%)	4/34 (12%)
Day of First Observation	672	665	603
Life Table Tests (e)	P=0.095N	P=0.101N	P=0.105N
Logistic Regression Tests (e)	P=0.076N	P=0.072N	P=0.089N
Cochran-Armitage Trend Test (e)	P=0.037N		
Fisher Exact Test (e)		P=0.073N	P=0.039N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) No P value is reported because no tumors were observed in the 25-ppm and control groups.

TABLE D4. HISTORICAL INCIDENCE OF HEPATOCELLULAR NEOPLASMS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/50	2/50	3/50
Methyl methacrylate	7/50	0/50	7/50
Propylene	0/50	2/50	2/50
1,2-Epoxybutane	2/50	2/50	4/50
Dichloromethane	2/50	1/50	3/50
Ethylene oxide	1/49	5/49	6/49
Bromoethane	3/50	2/50	5/50
Tetrachloroethylene	3/48	1/48	4/48
TOTAL	19/397 (4.8%)	15/397 (3.8%)	34/397 (8.6%)
SD (b)	4.28%	2.97%	3.37%
Range (c)			
High	7/50	5/49	7/50
Low	0/50	0/50	2/50
Overall Historical Incidence for Untreated Controls			
TOTAL	100/1,683 (5.9%)	(d) 68/1,683 (4.0%)	(d) 163/1,683 (9.7%)
SD (b)	3.75%	2.30%	4.25%
Range (c)			
High	8/49	4/48	10/49
Low	0/50	0/49	2/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one hepatoblastoma

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

	Chamber Control	10 ppm	25 ppm
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	48	49	50
ALIMENTARY SYSTEM			
Gallbladder	(38)	(2)	(42)
Dilatation	1 (3%)	1 (50%)	
Infiltration cellular, lymphocytic	2 (5%)		1 (2%)
Intestine large, cecum	(45)	(2)	(43)
Peyer's patch, hyperplasia, lymphoid	1 (2%)		1 (2%)
Intestine large, colon	(47)	(2)	(46)
Serosa, inflammation, chronic active, multifocal	1 (2%)		
Intestine small	(46)	(6)	(47)
Peyer's patch, hyperplasia, lymphoid	2 (4%)	1 (17%)	
Intestine small, duodenum	(45)	(3)	(44)
Serosa, ileum, jejunum, inflammation, chronic active, multifocal	1 (2%)		
Liver	(48)	(16)	(49)
Angiectasis, focal		1 (6%)	
Clear cell focus			1 (2%)
Cytomegaly, focal			1 (2%)
Eosinophilic focus	1 (2%)		
Fatty change, diffuse	1 (2%)		1 (2%)
Granuloma, multifocal	2 (4%)		
Hematocyst		1 (6%)	
Hematopoietic cell proliferation, multifocal	3 (6%)		1 (2%)
Hemorrhage, multifocal			1 (2%)
Hepatodiaphragmatic nodule	1 (2%)		
Infarct	1 (2%)		
Infiltration cellular, lymphocytic, diffuse	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	5 (10%)		3 (6%)
Infiltration cellular, mixed cell	1 (2%)		1 (2%)
Inflammation, subacute, multifocal	8 (17%)		5 (10%)
Necrosis, multifocal	2 (4%)		1 (2%)
Vacuolization cytoplasmic, diffuse	1 (2%)		
Vacuolization cytoplasmic, multifocal	1 (2%)		1 (2%)
Bile duct, hyperplasia, focal	1 (2%)		
Bile duct, hyperplasia, multifocal		1 (6%)	
Centrilobular, necrosis, diffuse	1 (2%)	1 (6%)	
Centrilobular, necrosis, multifocal	1 (2%)		
Portal, inflammation, chronic		1 (6%)	
Mesentery	(8)	(3)	(2)
Infiltration cellular, lymphocytic, multifocal	2 (25%)		
Infiltration cellular, mixed cell	2 (25%)		
Fat, necrosis, focal		1 (33%)	
Fat, necrosis, multifocal		2 (67%)	
Pancreas	(47)	(3)	(49)
Cytomegaly, multifocal	2 (4%)		
Hypertrophy, focal	1 (2%)		
Infiltration cellular, lymphocytic, focal	1 (2%)		1 (2%)
Infiltration cellular, lymphocytic, multifocal	9 (19%)		4 (8%)
Infiltration cellular, mixed cell, multifocal	1 (2%)		
Inflammation, chronic active	2 (4%)		1 (2%)
Acinus, atrophy	3 (6%)		2 (4%)
Pharynx	(1)		
Palate, ulcer, chronic	1 (100%)		
Salivary glands	(48)	(1)	(48)
Hyperplasia, lymphoid			1 (2%)
Infiltration cellular, lymphocytic, focal	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	32 (67%)		21 (44%)
Inflammation, chronic, focal			1 (2%)
Inflammation, chronic active, focal	1 (2%)		

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

	Chamber Control	10 ppm	25 ppm
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(47)	(3)	(45)
Hyperplasia, squamous, diffuse			1 (2%)
Inflammation, chronic active, focal	1 (2%)		
Stomach, glandular	(47)	(3)	(47)
Developmental malformation	1 (2%)		
Infiltration cellular, lymphocytic, multifocal			1 (2%)
Inflammation, chronic active, focal			1 (2%)
Tooth	(1)		(1)
Developmental malformation			1 (100%)
Pulp, inflammation, chronic active, focal	1 (100%)		
CARDIOVASCULAR SYSTEM			
Heart	(48)	(2)	(48)
Bacterium	1 (2%)		
Cardiomyopathy			2 (4%)
Inflammation, chronic active, multifocal	1 (2%)		
Aortic valve, thrombus	1 (2%)		
Atrium left, thrombus	1 (2%)		1 (2%)
Mitral valve, inflammation, chronic active, focal	1 (2%)		
Pericardium, infiltration cellular, mixed cell, multifocal	1 (2%)		
Valve, pigmentation, hemosiderin, multifocal	1 (2%)		
Ventricle, mineralization, focal	1 (2%)		
Ventricle, necrosis, subacute, focal	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(47)	(3)	(49)
Accessory adrenal cortical nodule	6 (13%)		2 (4%)
Capsule, hyperplasia, diffuse	13 (28%)	1 (33%)	12 (24%)
Capsule, hyperplasia, multifocal	33 (70%)	1 (33%)	32 (65%)
Capsule, inflammation, chronic active, focal	1 (2%)		
Adrenal gland, cortex	(47)	(2)	(47)
Angiectasis, multifocal			1 (2%)
Atrophy, focal			1 (2%)
Degeneration, fatty, focal	2 (4%)		
Hyperplasia, focal	1 (2%)		2 (4%)
Hypertrophy, focal	1 (2%)		1 (2%)
Medulla, hematopoietic cell proliferation, multifocal	1 (2%)		
Adrenal gland, medulla	(45)	(2)	(47)
Amyloid deposition			1 (2%)
Hyperplasia, focal	2 (4%)		1 (2%)
Islets, pancreatic	(47)	(3)	(49)
Atrophy, multifocal	1 (2%)		1 (2%)
Hyperplasia, multifocal	7 (15%)	1 (33%)	3 (6%)
Parathyroid gland	(29)	(1)	(25)
Infiltration cellular, lymphocytic, focal	1 (3%)		2 (8%)
Pituitary gland	(46)	(5)	(47)
Pars distalis, angiectasis, focal	7 (15%)		
Pars distalis, hyperplasia, focal	4 (9%)		
Pars distalis, hyperplasia, multifocal	1 (2%)		
Pars distalis, hypertrophy, focal	1 (2%)		
Thyroid gland	(48)	(2)	(42)
Infiltration cellular, lymphocytic, focal	1 (2%)		
Inflammation, chronic active, focal	1 (2%)		
Follicle, cyst	1 (2%)		2 (5%)
Follicular cell, hyperplasia, focal	1 (2%)		
Follicular cell, hyperplasia, multifocal	2 (4%)		1 (2%)

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

	Chamber Control	10 ppm	25 ppm
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(1)		(1)
Cyst, multifocal			1 (100%)
Ovary	(46)	(14)	(44)
Abscess, multiple	1 (2%)	1 (7%)	
Angiectasis			1 (2%)
Atrophy	1 (2%)		
Cyst	9 (20%)	9 (64%)	4 (9%)
Hemorrhage, focal	2 (4%)		
Hyperplasia, diffuse			1 (2%)
Infiltration cellular, lymphocytic	2 (4%)	1 (7%)	
Thrombus	1 (2%)		
Periovarian tissue, infiltration cellular, lymphocytic	4 (9%)		
Uterus	(48)	(37)	(45)
Abscess, single	1 (2%)		
Adenomyosis	1 (2%)		
Angiectasis	1 (2%)		
Dilatation	2 (4%)	5 (14%)	12 (27%)
Hemorrhage, acute	1 (2%)		
Hyperplasia, cystic	36 (75%)	29 (78%)	29 (64%)
Inflammation, chronic, diffuse			1 (2%)
Inflammation, chronic active, multifocal	1 (2%)		
Metaplasia, squamous			1 (2%)
Thrombus	1 (2%)		
Serosa, cyst	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(47)	(2)	(47)
Hypoplasia, focal			1 (2%)
Myeloid cell, hyperplasia	1 (2%)		
Lymph node	(48)	(8)	(49)
Hyperplasia, lymphoid	1 (2%)		
Bronchial, depletion lymphoid, diffuse	1 (2%)		
Bronchial, hyperplasia, lymphoid			2 (4%)
Bronchial, hyperplasia, plasma cell	1 (2%)		1 (2%)
Mediastinal, hemorrhage	1 (2%)		
Mediastinal, hyperplasia, lymphoid			2 (4%)
Mediastinal, hyperplasia, plasma cell	1 (2%)		
Lymph node, mandibular	(45)	(1)	(43)
Hyperplasia, lymphoid	4 (9%)		3 (7%)
Hyperplasia, plasma cell	3 (7%)		
Hyperplasia, re cell	1 (2%)		1 (2%)
Infiltration cellular, polymorphonuclear, diffuse	1 (2%)		
Pigmentation, hemosiderin, diffuse	1 (2%)		2 (5%)
Lymph node, mesenteric	(38)	(6)	(32)
Hematopoietic cell proliferation		2 (33%)	
Hemorrhage	3 (8%)	3 (50%)	
Hyperplasia, lymphoid	4 (11%)		
Hyperplasia, plasma cell	1 (3%)		
Hyperplasia, re cell	1 (3%)		
Spleen	(47)	(13)	(49)
Angiectasis	1 (2%)		
Congestion			1 (2%)
Depletion lymphoid			2 (4%)
Developmental malformation			1 (2%)

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

	Chamber Control	10 ppm	25 ppm
HEMATOPOIETIC SYSTEM			
Spleen (Continued)	(47)	(13)	(49)
Hematopoietic cell proliferation	6 (13%)	6 (46%)	
Hyperplasia, lymphoid	6 (13%)		2 (4%)
Hyperplasia, plasma cell			1 (2%)
Infarct	1 (2%)		1 (2%)
Pigmentation, hemosiderin	3 (6%)		
Capsule, abscess, chronic	1 (2%)		
Capsule, ectopic tissue	1 (2%)		
Capsule, fibrosis, focal	1 (2%)		
Thymus	(40)	(2)	(42)
Angiectasis, multifocal			1 (2%)
Cyst, multiple			1 (2%)
Depletion lymphoid	3 (8%)		2 (5%)
Ectopic parathyroid gland	2 (5%)		2 (5%)
Hyperplasia, lymphoid	1 (3%)		3 (7%)
Epithelial cell, hyperplasia	1 (3%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(1)	(44)
Ectasia, multifocal	1 (2%)		1 (2%)
Hyperplasia, diffuse	2 (4%)		
Infiltration cellular, mixed cell, multifocal	1 (2%)		
Inflammation, chronic, diffuse	1 (2%)		
Inflammation, chronic active, diffuse	1 (2%)		
Skin	(46)	(20)	(47)
Infiltration cellular, lymphocytic, focal	1 (2%)		
Inflammation, chronic, diffuse	1 (2%)		
Inflammation, chronic active, diffuse	1 (2%)		2 (4%)
Subcutaneous tissue, edema	1 (2%)	1 (5%)	
Subcutaneous tissue, hemorrhage, acute		1 (5%)	
MUSCULOSKELETAL SYSTEM			
Bone	(47)	(12)	(47)
Fibrous osteodystrophy	7 (15%)	10 (83%)	8 (17%)
Joint, inflammation, chronic, focal	1 (2%)		
NERVOUS SYSTEM			
Brain	(48)	(2)	(49)
Hemorrhage, acute, focal	1 (2%)		
Hydrocephalus	1 (2%)		
Inflammation, acute, focal	1 (2%)		
Mineralization, multifocal	29 (60%)	1 (50%)	16 (33%)
RESPIRATORY SYSTEM			
Larynx	(40)	(1)	(40)
Inflammation, chronic	1 (3%)		
Inflammation, chronic active	2 (5%)		
Lung	(48)	(49)	(49)
Crystals		4 (8%)	1 (2%)
Edema			1 (2%)
Infiltration cellular, lymphocytic, multifocal	9 (19%)	10 (20%)	7 (14%)
Infiltration cellular, histiocytic, diffuse	2 (4%)		2 (4%)
Infiltration cellular, histiocytic, focal	1 (2%)	4 (8%)	
Infiltration cellular, histiocytic, multifocal		6 (12%)	4 (8%)
Infiltration cellular, mixed cell, diffuse	1 (2%)		
Inflammation, chronic active, focal		1 (2%)	
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)
Alveolus, inflammation, chronic active, focal			1 (2%)

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

	Chamber Control	10 ppm	25 ppm
RESPIRATORY SYSTEM			
Lung (Continued)	(48)	(49)	(49)
Alveolus, inflammation, chronic active, multifocal		1 (2%)	1 (2%)
Artery, inflammation, acute, multifocal	1 (2%)		
Bronchiole, hyperplasia, focal		1 (2%)	
Bronchiole, hyperplasia, multifocal		1 (2%)	
Bronchiole, inflammation, chronic active, focal			1 (2%)
Bronchiole, alveolus, inflammation, chronic active, focal		5 (10%)	1 (2%)
Bronchiole, alveolus, inflammation, chronic active, multifocal		9 (18%)	35 (71%)
Mediastinum, infiltration cellular, lymphocytic, multifocal	2 (4%)		
Peribronchiolar, inflammation, chronic active, multifocal	1 (2%)		
Pleura, inflammation, chronic active, multifocal	1 (2%)		
Nose	(48)	(49)	(48)
Exudate		2 (4%)	
Foreign body	1 (2%)		
Lumen, crystals			3 (6%)
Mucosa, inflammation, chronic	1 (2%)		
Mucosa, inflammation, chronic active	3 (6%)	49 (100%)	47 (98%)
Nasolacrimal duct, hyperplasia			1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)		
Nasolacrimal duct, inflammation, chronic	3 (6%)		2 (4%)
Olfactory epithelium, atrophy, focal	1 (2%)		
Respiratory epithelium, hyperplasia	5 (10%)	49 (100%)	47 (98%)
Trachea	(48)	(2)	(47)
Edema			1 (2%)
Inflammation, chronic	1 (2%)		
Metaplasia, squamous, multifocal			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(2)		
Atrophy	1 (50%)		
Cornea, neovascularization	1 (50%)		
Lacrimal gland	(10)		(5)
Infiltration cellular, lymphocytic	1 (10%)		
Infiltration cellular, lymphocytic, focal	1 (10%)		2 (40%)
Infiltration cellular, lymphocytic, multifocal	6 (60%)		2 (40%)
Infiltration cellular, mixed cell, multifocal	1 (10%)		
URINARY SYSTEM			
Kidney	(48)	(7)	(49)
Cyst	1 (2%)		
Infiltration cellular, lymphocytic, multifocal	22 (46%)		7 (14%)
Capsule, inflammation, chronic active	2 (4%)		
Cortex, regeneration, multifocal			2 (4%)
Cortex, epithelium, hyperplasia, atypical, multifocal			1 (2%)
Medulla, epithelium, karyomegaly, multifocal	1 (2%)		
Urinary bladder	(45)	(2)	(40)
Infiltration cellular, lymphocytic, focal	2 (4%)		3 (8%)
Infiltration cellular, lymphocytic, multifocal	19 (42%)		9 (23%)
Infiltration cellular, mixed cell, multifocal	1 (2%)		1 (3%)
Perforation			1 (3%)
Serosa, inflammation, chronic	1 (2%)		2 (5%)

APPENDIX E

RESULTS OF SEROLOGIC ANALYSIS

APPENDIX E. RESULTS OF SEROLOGIC ANALYSIS

Methods

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

Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

Results

No positive titers were observed in any of the control animals tested at the end of the studies.

APPENDIX F

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

Pellet Diet: October 1981 to October 1983

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.5 ± 0.73	22.2-24.9	25
Crude fat (percent by weight)	4.9 ± 0.54	3.3-5.7	25
Crude fiber (percent by weight)	3.3 ± 0.25	2.9-3.8	25
Ash (percent by weight)	6.5 ± 0.46	5.7-7.31	25
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	12,052 ± 4,522	4,100-24,000	25
Vitamin D (IU/kg)	4,650 ± 2,333	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.4 ± 2.17	13.0-21.0	25
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.20	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200-3,430	4
Minerals			
Calcium (percent)	1.27 ± 0.11	1.11-1.44	25
Phosphorus (percent)	0.98 ± 0.05	0.88-1.1	25
Potassium (percent)	0.862 ± 0.10	0.772-0.970	3
Chloride (percent)	0.546 ± 0.10	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four lots of feed analyzed for nutrients reported in this table were manufactured during 1983-85.

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.13	0.27-0.77	25
Cadmium (ppm) (a)	<0.1		25
Lead (ppm)	0.80 ± 0.64	0.33-3.37	25
Mercury (ppm) (a)	<0.05		25
Selenium (ppm)	0.29 ± 0.06	0.14-0.38	25
Aflatoxins (ppb) (a)	<5		25
Nitrate nitrogen (ppm) (b)	9.2 ± 4.7	0.1-22.0	25
Nitrite nitrogen (ppm) (b)	2.3 ± 1.92	<0.1-7.2	25
BHA (ppm) (c)	5.1 ± 4.9	2.0-17.0	25
BHT (ppm) (c)	2.9 ± 2.7	<1.0-12.0	25
Aerobic plate count (CFU/g) (d)	44,180 ± 35,870	5,500-130,000	25
Coliform (MPN/g) (e,f)	11.5 ± 20.1	<3-93	24
Coliform (MPN/g) (g)	32.8 ± 91.7	<3-460	25
E. coli (MPN/g) (h)	<3		25
Total nitrosamines (ppb) (i)	4.0 ± 2.6	0.8-9.3	25
N-Nitrosodimethylamine (ppb) (i)	3.1 ± 2.5	0.8-8.3	25
N-Nitrosopyrrolidine (ppb)	1.14 ± 0.47	0.9-2.9	25
Pesticides (ppm)			
α-BHC (a,j)	<0.01		25
β-BHC (a)	<0.02		25
γ-BHC (a)	<0.01		25
δ-BHC (a)	<0.01		25
Heptachlor (a)	<0.01		25
Aldrin (a)	<0.01		25
Heptachlor epoxide (a)	<0.01		25
DDE (a)	<0.01		25
DDD (a)	<0.01		25
DDT (a)	<0.01		25
HCB (a)	<0.01		25
Mirex (a)	<0.01		25
Methoxychlor (k)	<0.05	0.06 (7/26/83)	25
Dieldrin (a)	<0.01		25
Endrin (a)	<0.01		25
Telodrin (a)	<0.01		25
Chlordane (a)	<0.05		25
Toxaphene (a)	<0.1		25
Estimated PCBs (a)	<0.2		25
Ronnel (a)	<0.01		25
Ethion (a)	<0.02		25
Trithion (a)	<0.05		25
Diazinon (a)	<0.1		25
Methyl parathion (a)	<0.02		25
Ethyl parathion (a)	<0.02		25
Malathion (l)	0.10 ± 0.10	<0.05-0.45	25
Endosulfan I (m)	<0.01		23
Endosulfan II (m)	<0.01		23
Endosulfan sulfate (m)	<0.03		23

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

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) Mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained for the lot produced on September 23, 1982.
(g) Mean, standard deviation, and range include the high value given in footnote (g).
(h) All values were less than 3 MPN/g.
(i) All values were corrected for percent recovery.
(j) BHC = hexachlorocyclohexane or benzene hexachloride
(k) One observation was above the detection limit. The value and the date it was obtained are given under the range.
(l) Twelve lots contained more than 0.05 ppm.
(m) Two lots (October 26, 1981, and November 25, 1981) were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX G

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

APPENDIX G. CHEMICAL CHARACTERIZATION

PROCUREMENT AND CHARACTERIZATION OF VINYL TOLUENE

Vinyl toluene (mixed isomers), referred to in this Technical Report as vinyl toluene, was manufactured by Dow Chemical Company (Midland, MI). One lot was obtained from Missouri Solvents and Chemical Company, and two lots were obtained from Chem Central (Table G1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the vinyl toluene studies are on file at the National Institute of Environmental Health Sciences.

The identity of all lots as a mixture of *m*-vinyl toluene and *p*-vinyl toluene was confirmed by spectroscopic analyses. The infrared and ultraviolet/visible spectra agreed with the literature spectra (Sadtler Standard Spectra); the nuclear magnetic resonance spectrum was consistent with that expected for a mixture of *m*-vinyl toluene and *p*-vinyl toluene (representative spectra are presented in Figures G1 and G2).

The purity of all lots was determined by elemental analysis, Karl Fischer water analysis, the American Society for Testing and Materials (ASTM) visual turbidity test for polymers in styrene (limit of detection, 0.001% polymer), semiquantitative determination of the *t*-butylcatechol inhibitor by visual color comparison after the addition of 1 N sodium hydroxide, and gas chromatography. Gas chromatography was performed with flame ionization detection, a nitrogen carrier, and either a GP 5% SP1200/1.75% Bentone 34 column (system 1) or a helium carrier and a Grade AA Carbowax 20M capillary column (system 2). The vinyl toluene isomers were quantitated with system 1 against a standard solution of *p*-vinyl toluene, with *o*-xylene as an internal standard. The *m*-isomer was quantitated by a comparison of peak areas with the *p*-isomer.

The results of elemental analysis of lot no. CH910 were in agreement with the theoretical value for carbon and were slightly low for hydrogen. Karl Fischer analysis indicated the presence of 0.015% water. *t*-Butylcatechol was present at approximately 70 ppm. No observable polymer was present. Gas chromatography with system 1 indicated two major peaks and six impurities, four before and two after the major peaks. *p*-Vinyl toluene and *m*-vinyl toluene represented 31.6% and 68.4%, respectively, of the mixture. The area of impurity peaks totaled 0.22% of the combined area of the two major peaks. Gas chromatography by system 2 did not resolve the *m*- and *p*-isomers. Fourteen impurities, 8 before and 6 after the major peak, totaled 0.64% of the major peak area.

TABLE G1. IDENTITY AND SOURCE OF VINYL TOLUENE USED IN THE INHALATION STUDIES

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers		
CH910	CH910	CC012981; C010483
Date of Initial Use		
8/20/80		12/1/81; 8/4/83
Supplier (a)		
Missouri Solvents and Chemical Company (Kansas City, MO)	Same as 15-d studies	Chem Central (Dallas, TX)

(a) Dow Chemical Co. (Midland, MI) was the manufacturer of all lots.

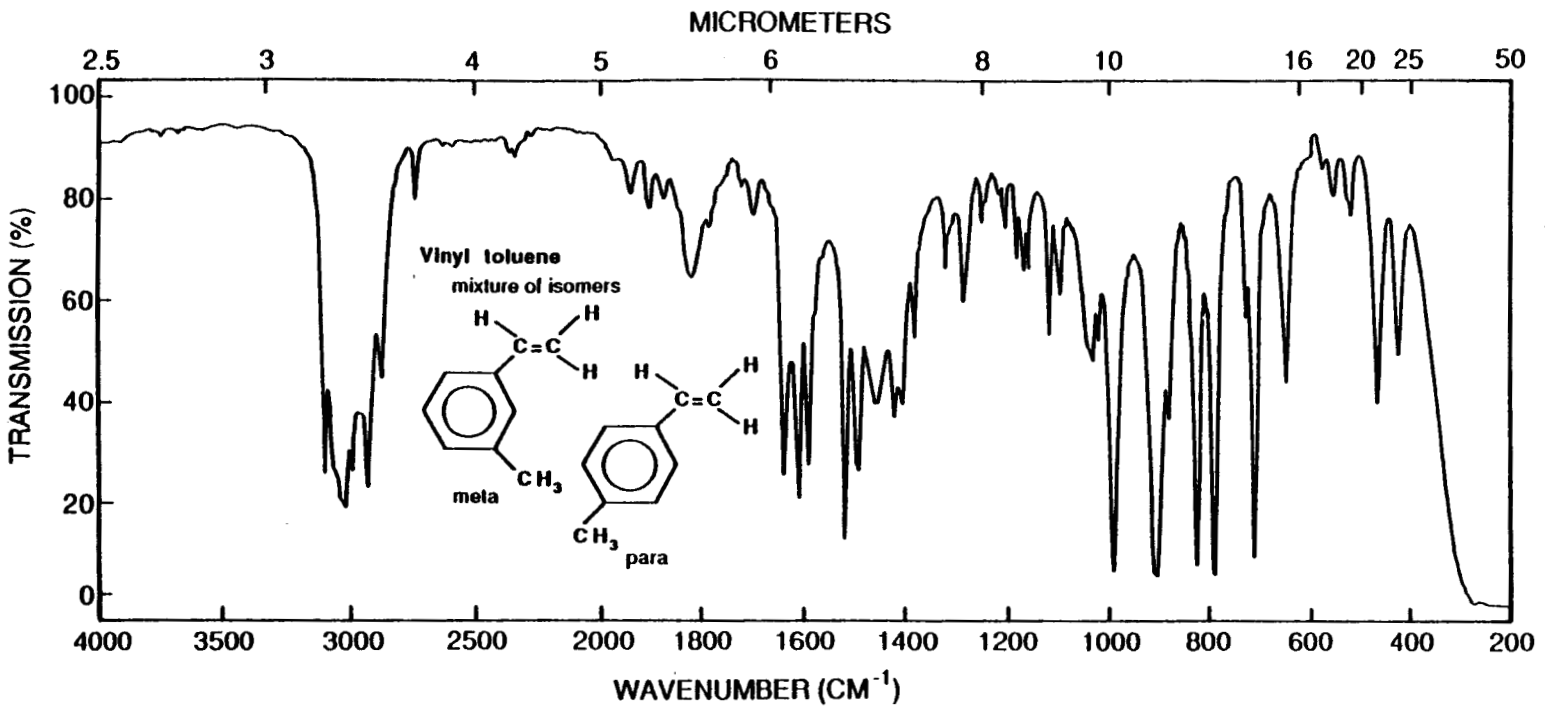

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF VINYL TOLUENE (LOT NO. CC012981)

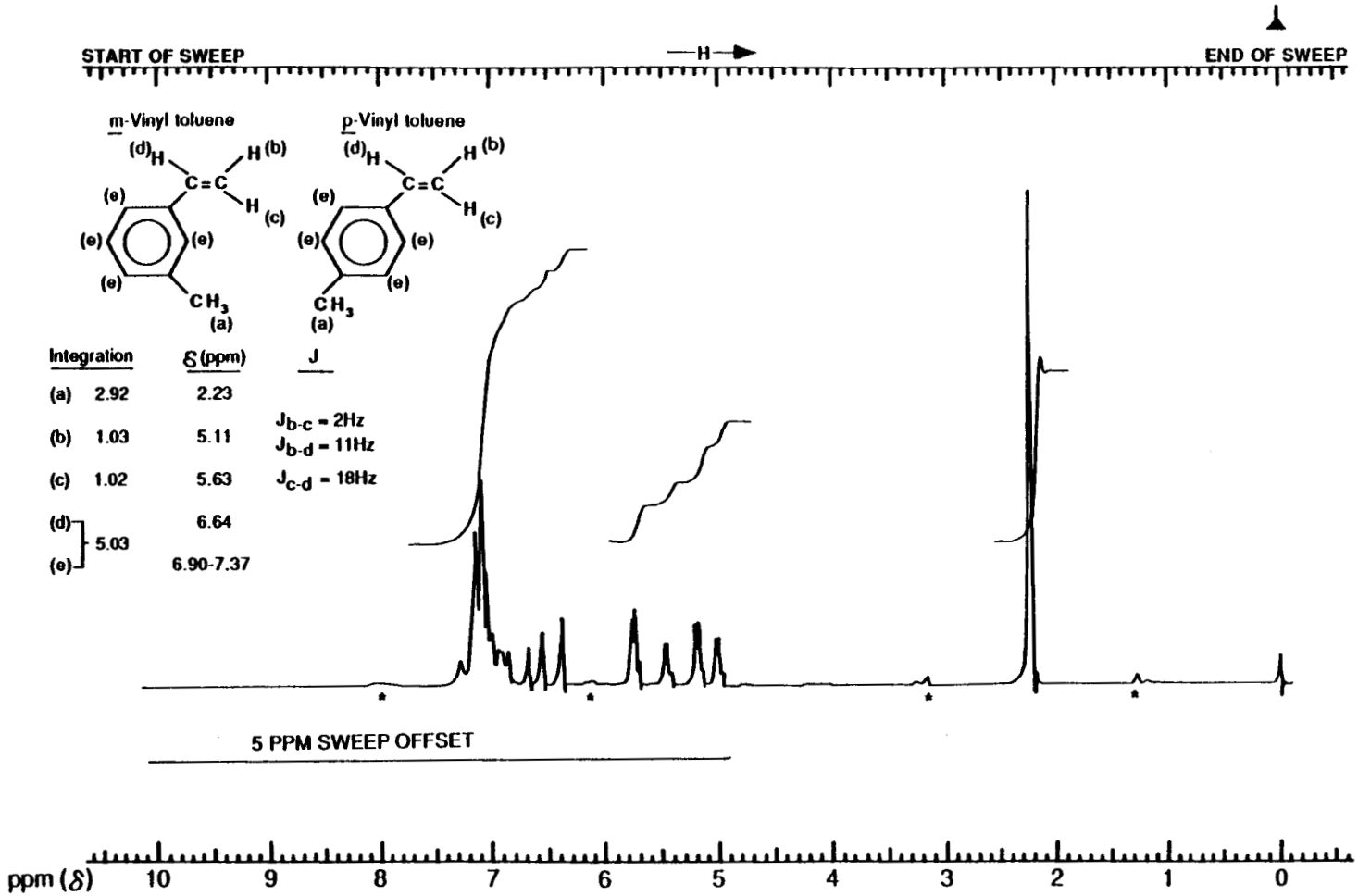

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF VINYL TOLUENE (LOT NO. CC012981)

The results of elemental analysis of lot no. CC012981 were in agreement with the theoretical values for carbon and hydrogen. Karl Fischer analysis indicated the presence of 0.026% water. *t*-Butylcatechol was present at approximately 30 ppm. No observable polymer was present. Gas chromatography with system 1 indicated two major peaks and five impurities, four before and one after the major peaks. *p*-Vinyl toluene and *m*-vinyl toluene represented 35.0% and 64.8% of the material, respectively. The area of impurity peaks totaled 0.55% of the combined area of the major peaks. Gas chromatography with system 2 did not resolve the *m*- and *p*-isomers; 11 impurities were observed, 8 before and 3 after the major peak, with a combined relative area of 0.72%.

The results of elemental analysis of lot no. C010483 were in agreement with the theoretical values for carbon and hydrogen. Karl Fischer analysis indicated the presence of 0.0086% water. *t*-Butylcatechol was present at approximately 30 ppm. No observable polymer was present. Gas chromatography with system 1 indicated two major peaks and four impurities, three before and one after the major peaks. *p*-Vinyl toluene and *m*-vinyl toluene represented 31.5% and 71.4% of the material, respectively. The combined relative area of the four impurities totaled 0.27%. Gas chromatography with system 2 did not resolve the *m*- and *p*-isomers. Ten impurities were observed, totaling 0.59% of the major peak area.

Stability studies performed by gas chromatography with the same column as previously described for system 1, with *o*-xylene as an internal standard, indicated that vinyl toluene was stable as a bulk chemical when stored protected from light for 2 weeks at temperatures up to 25° C. Results of periodic analysis by infrared spectroscopy, gas chromatography, determination of inhibitor concentration, and polymer concentration indicated no significant degradation of the study material throughout the studies.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Vapor Generation System

During the short-term studies, vinyl toluene was metered from a reservoir via a precision pump into a J-tube containing ¼-inch glass beads. Compressed air, heated to 150°-160° C for the 15-day studies or 60°-70° C for the 13-week studies, was passed through the system. The vinyl toluene vapor then entered the airstream at the top of the chamber (Hazleton 2000®, Lab Products, Inc.) and was mixed in the chamber plenum before entering the exposure area of the chamber. During the 2-year studies, the 100- and 300-ppm vapor generation systems were the same as previously described for the 13-week studies. For the 10- and 25-ppm generation systems, dry filtered air at ambient temperature was precisely metered, via needle valves, through small type C sintered glass frits immersed in liquid vinyl toluene contained in gas dispersion bottles. Vinyl toluene vapor was transported with carrier air into secondary flasks where it was further diluted with filtered air, mixed, and then channeled to the appropriate intake port of the study chambers (Table G2). An individual generator was used for each chamber.

TABLE G2. GENERATION OF CHAMBER CONCENTRATIONS IN THE INHALATION STUDIES OF VINYL TOLUENE

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies (rats)	Two-Year Studies (mice)
The liquid chemical was metered into a vaporization system. Heated compressed air at 150°-160° C was delivered at 30-50 liters/min by a heat torch into the system.	Same as 15-d studies. Air was heated to 60°-70° C.	Same as 15-d studies. Air was heated to 70° C.	Dry filtered air at ambient temperature was metered through liquid chemical. Vinyl toluene vapor and air were transferred to secondary flasks and then to the intake port of the study chamber via Teflon® lines.

Vapor Concentration Monitoring

The concentration of vinyl toluene in the chambers and the exposure room was monitored by an automatic sampling system coupled to a gas chromatograph (Varian 2700) equipped with a flame ionization detector and a 3% SP2250 column (100% Carbowax 20M-TPA column for the short-term studies). The chromatographic conditions during the 2-year studies involved the use of a nitrogen carrier at 30 ml/minute and injector, column oven, and detector temperatures of 200° C, 75° C, and 250° C, respectively. The gas chromatographic system was standardized daily by manually injecting prepared solutions of vinyl toluene in *n*-hexane. Samples from the study chamber atmospheres were pulled by a vacuum pump from the chambers. A series of valves controlled by a hard-wired program directed the samples either to the gas chromatographic system or to the exhaust. Flow through all sampling lines was continuous. During the 2-year studies, each study chamber atmosphere, a sample of the control chamber atmosphere, and a sample of workroom air were analyzed every 30 minutes. The distribution of the mean daily concentrations in the chambers is summarized in Table G3.

TABLE G3. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF VINYL TOLUENE DURING THE TWO-YEAR INHALATION STUDIES

Range of Concentration (percent of target)	Number of Days Mean Within Range			
	10 ppm	25 ppm	100 ppm	300 ppm
>120	3	1	0	0
110-120	20	8	13	3
90-110	466	485	479	489
80-90	8	3	4	2
<80	1	1	0	0
Not exposed (a)	4	4	3	5

(a) Number of days animals not exposed because of equipment failure or analytical malfunctions

APPENDIX H

GENETIC TOXICOLOGY

OF VINYL TOLUENE

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1987) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

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

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 100 µg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

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

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was performed without S9.

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

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

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

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

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

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

RESULTS

Vinyl toluene did not induce gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in a preincubation protocol at doses up to 1,000 µg/plate with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Zeiger et al., 1987; Table H1). In the mouse lymphoma assay for induction of Tft resistance in L5178Y cells, vinyl toluene gave a positive response in two trials conducted without S9 at the highest doses tested; these doses also produced severe toxicity, as evidenced by a relative total growth of less than 10% (McGregor et al., 1988; Table H2). Vinyl toluene was not tested in the mouse lymphoma assay with S9. In cytogenetic tests with CHO cells, vinyl toluene did not induce SCEs or chromosomal aberrations in either the presence or the absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables H3 and H4).

TABLE H1. MUTAGENICITY OF VINYL TOLUENE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+10% S9 (hamster) Trial 1	+10% S9 (hamster) Trial 2	+10% S9 (rat) Trial 1	+10% S9 (rat) Trial 2
TA100	0	151 ± 10.0	137 ± 7.4	216 ± 9.3	140 ± 7.5	214 ± 9.7	146 ± 8.1
	1	--	--	--	--	--	129 ± 5.7
	3.3	--	119 ± 4.7	216 ± 4.4	167 ± 7.9	190 ± 7.8	124 ± 4.7
	10	169 ± 3.2	132 ± 12.7	213 ± 7.1	170 ± 9.5	202 ± 10.1	130 ± 4.0
	33	163 ± 7.1	122 ± 3.2	216 ± 23.8	171 ± 3.2	227 ± 12.0	141 ± 5.8
	100	157 ± 25.9	132 ± 1.7	222 ± 3.3	168 ± 11.5	220 ± 11.7	128 ± 4.1
	333	165 ± 12.5	127 ± 10.1	189 ± 8.8	172 ± 6.0	Toxic	
	1,000	Toxic					
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,423 ± 77.5	1,254 ± 31.9	1,680 ± 64.7	2,507 ± 173.1	2,719 ± 231.9	2,265 ± 36.3
TA1535	0	17 ± 0.6	8 ± 1.8	18 ± 3.6	13 ± 0.3	19 ± 1.2	10 ± 1.2
	3.3	--	8 ± 0.0	24 ± 3.2	9 ± 1.0	25 ± 0.3	11 ± 2.0
	10	15 ± 2.4	8 ± 1.3	16 ± 2.6	11 ± 2.0	25 ± 2.1	10 ± 3.1
	33	19 ± 0.9	7 ± 1.0	20 ± 0.6	12 ± 2.6	14 ± 4.9	10 ± 2.5
	100	17 ± 4.0	7 ± 1.5	15 ± 1.2	10 ± 1.8	18 ± 4.2	11 ± 1.5
	333	1 ± 0.9	2 ± 0.7	18 ± 4.0	12 ± 1.7	29 ± 1.0	10 ± 2.3
	1,000	0 ± 0.0					
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		699 ± 72.5	642 ± 9.8	406 ± 53.2	253 ± 16.7	278 ± 44.0	209 ± 7.0
TA1537	0	11 ± 3.5	5 ± 1.0	15 ± 0.9	9 ± 2.3	15 ± 1.8	11 ± 1.3
	1	--	--	--	--	6 ± 0.9	--
	3.3	--	5 ± 0.3	11 ± 0.7	9 ± 1.2	12 ± 2.3	6 ± 0.6
	10	18 ± 0.3	4 ± 1.0	15 ± 1.5	6 ± 1.8	16 ± 0.9	8 ± 0.9
	33	15 ± 0.9	3 ± 0.3	11 ± 1.2	8 ± 1.5	12 ± 2.7	5 ± 1.3
	100	11 ± 2.3	4 ± 1.2	15 ± 1.2	6 ± 0.9	14 ± 2.3	7 ± 1.0
	333	2 ± 0.7	2 ± 0.3	10 ± 2.7	8 ± 2.0	Toxic	
	1,000	0 ± 0.0					
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		465 ± 44.5	253 ± 68.4	173 ± 10.0	226 ± 55.7	211 ± 8.8	185 ± 39.6
TA98	0	19 ± 1.7	13 ± 2.9	38 ± 3.3	17 ± 0.9	30 ± 5.7	24 ± 2.6
	3.3	--	9 ± 1.9	30 ± 5.7	17 ± 1.2	32 ± 4.9	18 ± 1.5
	10	16 ± 3.0	8 ± 0.0	45 ± 2.7	16 ± 2.5	40 ± 2.2	14 ± 0.9
	33	24 ± 2.4	10 ± 1.5	40 ± 3.0	17 ± 3.2	35 ± 3.0	10 ± 2.0
	100	22 ± 2.5	9 ± 1.5	43 ± 1.5	12 ± 0.7	36 ± 4.3	17 ± 4.0
	333	16 ± 1.3	8 ± 1.2	34 ± 4.2	9 ± 0.9	26 ± 2.8	6 ± 1.0
	1,000	Toxic					
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		182 ± 24.9	357 ± 36.5	553 ± 64.6	1,542 ± 45.0	391 ± 44.1	1,545 ± 112.3

(a) Study performed at Case Western Reserve University. The detailed protocol is presented in Zeiger et al. (1987). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY VINYL TOLUENE IN MOUSE L5178Y/TK LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Dimethyl sulfoxide		80.3 ± 11.3	100.3 ± 13.0	96.8 ± 10.8	42.8 ± 7.0
Vinyl toluene	12.5	54.0 ± 1.0	71.0 ± 13.0	88.0 ± 13.0	54.0 ± 7.0
	25	70.0 ± 3.0	88.5 ± 0.5	99.5 ± 11.5	47.5 ± 3.5
	50	70.5 ± 0.5	69.0 ± 7.0	123.5 ± 14.5	58.5 ± 6.5
	100	Lethal	--	--	--
Methyl methanesulfonate	15	27.0 ± 4.0	22.0 ± 5.0	559.5 ± 33.5	(d) 708.0 ± 145.0
Trial 2					
Dimethyl sulfoxide (e)		65.5 ± 2.1	100.0 ± 3.6	137.5 ± 5.7	70.5 ± 4.6
Vinyl toluene	10	65.0 ± 8.0	100.0 ± 9.0	120.5 ± 9.5	62.0 ± 3.0
	(f) 20	68.3 ± 3.4	66.0 ± 3.5	134.7 ± 7.5	66.3 ± 5.3
	(f) 40	60.7 ± 0.9	34.7 ± 5.5	185.7 ± 10.5	102.0 ± 5.0
	60	45.5 ± 5.5	5.5 ± 0.5	417.0 ± 2.0	(d) 311.0 ± 40.0
	(f) 80	Lethal	--	--	--
Methyl methanesulfonate	15	23.0 ± 2.0	19.5 ± 0.5	255.0 ± 8.0	(d) 378.5 ± 49.5
Trial 3					
Dimethyl sulfoxide (f)		68.3 ± 7.9	100.0 ± 6.8	110.7 ± 17.5	54.0 ± 2.3
Vinyl toluene	(f) 40	58.3 ± 6.2	65.0 ± 7.1	47.3 ± 6.2	28.3 ± 6.4
	(f) 45	62.0 ± 6.6	55.7 ± 5.5	62.7 ± 9.8	33.3 ± 2.2
	(f) 50	65.7 ± 5.7	35.7 ± 2.9	61.7 ± 8.1	31.3 ± 2.2
	(f) 55	69.3 ± 11.4	29.3 ± 4.4	79.0 ± 13.9	38.3 ± 3.2
	(f) 60	54.3 ± 5.8	8.0 ± 1.0	240.3 ± 54.8	(d) 146.3 ± 29.6
	(f) 65	Lethal	--	--	--
Methyl methanesulfonate	15	20.5 ± 3.5	17.0 ± 3.0	165.0 ± 20.0	(d) 283.5 ± 79.5

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by McGregor et al. (1988) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate, unless otherwise indicated; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(e) Data presented are the results of four tests.

(f) Data presented are the results of three tests.

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY VINYL TOLUENE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,046	461	0.44	9.2	27.0	
Vinyl toluene	1.6	50	1,043	442	0.42	8.8	27.0	95.7
	5	50	1,046	431	0.41	8.6	27.0	93.5
	16	50	1,049	457	0.44	9.1	27.0	98.9
	50	50	1,048	431	0.41	8.6	27.0	93.5
Mitomycin C	0.001	50	1,047	719	0.69	14.4	27.0	156.5
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,045	459	0.44	9.2	26.0	
Vinyl toluene	5	50	1,049	431	0.41	8.6	26.0	93.5
	10	50	1,042	454	0.44	9.1	26.0	98.9
	25	6	125	54	0.43	9.0	26.0	97.8
	50	50	1,049	441	0.42	8.8	26.0	95.7
	75	50	1,043	467	0.45	9.3	26.0	101.1
	100	0	--	--	--	--	--	--
	150	2	42	30	0.71	15.0	26.0	163.0
Mitomycin C	0.0008	10	205	118	0.58	11.8	26.0	128.3
	0.005	10	209	318	1.52	31.8	26.0	345.7
Trial 3--Summary: Negative								
Dimethyl sulfoxide		50	1,046	480	0.46	9.6	26.0	
Vinyl toluene	25	50	1,046	516	0.49	10.3	26.0	107.3
	50	50	1,046	459	0.44	9.2	26.0	95.8
	75	50	1,041	485	0.47	9.7	(d) 35.5	101.0
	100	50	1,041	554	0.53	11.1	(d) 35.5	115.6
Mitomycin C	0.0008	50	1,047	641	0.61	12.8	26.0	133.3
	0.005	10	209	310	1.48	31.0	26.0	322.9
+S9 (e)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,046	392	0.37	7.8	26.0	
Vinyl toluene	5	50	1,049	388	0.37	7.8	26.0	100.0
	16	50	1,041	420	0.40	8.4	26.0	107.7
	50	50	1,043	367	0.35	7.3	26.0	93.6
Cyclophosphamide	0.3	50	1,047	708	0.68	14.2	26.0	182.1
	0.6	10	210	208	0.99	20.8	26.0	266.72

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY VINYL TOLUENE (Continued)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
+S9 (e)								
Trial 2--Summary: Negative								
Dimethyl sulfoxide		50	1,039	403	0.39	8.1	26.0	
Vinyl toluene	10	50	1,041	402	0.39	8.0	26.0	98.8
	25	50	1,045	360	0.34	7.2	26.0	88.9
	50	50	1,034	440	0.43	8.8	26.0	108.6
	75	50	1,040	410	0.39	8.2	26.0	101.2
Cyclophosphamide	0.3	50	1,046	562	0.54	11.2	26.0	138.3
	0.6	10	210	142	0.68	14.2	26.0	175.3

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

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY VINYL TOLUENE (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 12.0 h					Harvest time: 13.3 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.0	0.0		100	1	0.01	1.0
Vinyl toluene					Vinyl toluene				
1.6	100	1	0.01	1.0	5	100	1	0.01	1.0
5	100	2	0.02	2.0	16	100	1	0.01	1.0
16	100	0	0.00	0.0	50	100	0	0.00	0.0
50	100	2	0.02	2.0					
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.125	100	5	0.05	5.0	15	100	10	0.10	10.0
0.25	100	27	0.27	19.0	50	50	28	0.56	48.0

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

APPENDIX I

LIVER WEIGHTS OF RATS AND MICE IN THE FIFTEEN-DAY AND THIRTEEN-WEEK INHALATION STUDIES OF VINYL TOLUENE

TABLE I1. LIVER WEIGHTS OF RATS IN THE FIFTEEN-DAY INHALATION STUDIES OF VINYL TOLUENE (a)

Concentration (ppm)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Body Weight (mg/g)
MALE				
0	5	211 ± 3	11,500 ± 400	54 ± 1.8
200	5	203 ± 2	11,500 ± 180	57 ± 0.4
400	5	**183 ± 3	**9,800 ± 230	53 ± 0.4
800	5	**183 ± 3	11,500 ± 270	**63 ± 0.4
1,300	5	**171 ± 2	*12,500 ± 180	**73 ± 0.9
FEMALE				
0	5	144 ± 1	7,400 ± 130	51 ± 0.4
200	5	**132 ± 1	7,100 ± 130	*54 ± 0.9
400	5	**129 ± 1	**5,700 ± 89	**44 ± 0.4
800	5	**131 ± 1	*6,800 ± 130	52 ± 0.4
1,300	5	**125 ± 1	**8,600 ± 180	**69 ± 1.3

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

TABLE I2. LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF VINYL TOLUENE (a)

Concentration (ppm)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Body Weight (mg/g)
MALE				
0	10	375 ± 10.5	14,809 ± 738	39.5 ± 1.66
25	10	375 ± 7.5	16,400 ± 710	43.6 ± 1.37
60	10	372 ± 6.5	15,998 ± 535	43.0 ± 1.29
160	10	353 ± 6.3	15,476 ± 581	43.8 ± 1.27
400	10	346 ± 8.7	15,139 ± 508	43.9 ± 1.51
1,000	10	**302 ± 9.8	15,950 ± 537	**52.9 ± 1.55
FEMALE				
0	10	214 ± 4.9	8,078 ± 483	38.0 ± 2.41
25	10	212 ± 4.3	8,239 ± 417	38.8 ± 1.55
60	10	209 ± 3.3	8,551 ± 296	41.0 ± 1.30
160	10	204 ± 1.2	8,227 ± 313	40.4 ± 1.54
400	10	201 ± 2.2	8,391 ± 525	41.7 ± 2.37
1,000	10	**189 ± 3.7	9,121 ± 236	**48.3 ± 1.51

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
**P<0.01

TABLE I3. LIVER WEIGHTS OF MICE IN THE FIFTEEN-DAY INHALATION STUDIES OF VINYL TOLUENE (a)

Concentration (ppm)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Body Weight (mg/g)
MALE				
0	5	26.4 ± 0.45	1,360 ± 36	52 ± 1.34
10	5	*27.8 ± 0.09	1,500 ± 40	54 ± 1.34
25	5	*27.6 ± 0.18	*1,530 ± 31	56 ± 1.34
50	5	26.0 ± 0.31	1,470 ± 31	57 ± 0.89
100	5	27.2 ± 0.31	1,510 ± 63	55 ± 1.79
200	2	26.5 ± 0.35	**1,720 ± 0	**65 ± 0.71
FEMALE				
0	5	24.8 ± 0.09	1,410 ± 18	57 ± 0.89
10	5	23.6 ± 0.45	**1,220 ± 40	**52 ± 1.34
25	5	24.8 ± 0.40	**1,220 ± 13	**49 ± 0.45
50	5	**22.6 ± 0.31	1,360 ± 22	60 ± 0.45
100	5	23.8 ± 0.27	**1,200 ± 22	**50 ± 0.89
200	5	23.6 ± 0.45	1,520 ± 54	**64 ± 1.34

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

TABLE I4. LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF VINYL TOLUENE (a)

Concentration (ppm)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Body Weight (mg/g)
MALE				
0	9	33.1 ± 0.70	1,547 ± 209	46.5 ± 6.13
10	5	33.4 ± 1.12	1,624 ± 64	48.7 ± 1.96
25	10	**29.1 ± 0.53	1,509 ± 56	52.0 ± 2.09
60	4	**29.0 ± 0.41	1,470 ± 62	50.7 ± 1.69
160	8	**26.5 ± 0.46	1,206 ± 71	45.6 ± 2.80
FEMALE				
0	10	27.6 ± 0.79	1,457 ± 94	52.9 ± 3.25
10	8	25.8 ± 0.56	1,343 ± 74	52.2 ± 2.89
25	10	**24.0 ± 0.39	1,231 ± 45	51.4 ± 1.88
60	10	**23.8 ± 0.36	*1,151 ± 78	48.3 ± 3.19
160	10	**23.2 ± 0.33	**1,088 ± 66	46.9 ± 2.77

(a) Mean ± standard error; P values vs. the controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

APPENDIX J

AUDIT SUMMARY

APPENDIX J. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report No. 375 for the 2-year studies of vinyl toluene in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives. The audit included review of:

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

Procedures and events for the exposure phase of the studies were documented adequately by records at the Archives. Review of the archival records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the generation, analysis, distribution, and delivery of doses to animals were complete and accurate.

Data entries on necropsy forms were made adequately. The thoroughness for observation of external potential masses for rats and mice combined were poor inlife (>69% of the external masses noted at necropsy had an inlife correlate) and good at necropsy (>95% of the external masses recorded inlife correlated with a necropsy observation). The date of death recorded at necropsy for each unscheduled-death animal had matching entries among the inlife records for 152/160 rats and 85/89 mice; the differences in date-of-death entries for 2 rats involved 3 months and 1 week, and the remaining 20 differences involved 1 day. The reason for animal removal recorded among the inlife records was in agreement with the disposition code recorded at necropsy for 299/300 rats and all mice. The condition code for each animal was consistent with the disposition code and gross observations assigned at necropsy.

An individual animal identifier (ear tag) was present and correct in the residual tissue bag for 61/62 rats and 45/45 mice examined. A total of 6 untrimmed potential lesions were found in the wet tissues of 45 mice examined, and none were found in those of 62 rats. Intestinal segments were opened adequately. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but 12 in rats and 6 in mice; after microscopic review of the slides involved in these noncorrelations,

only 3 were considered to be discrepencies. Blocks and slides were present, and corresponding tissue sections matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables. The P values and incidences of neoplasms given in the Technical Report were the same as those in the final pathology tables at the Archives.

This summary describes general audit findings and the extent to which data and factual information presented in the Technical Report are supported by records at the NTP Archives. Full details are presented in audit reports that are on file at the NIEHS.

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