NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 251

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COMMERCIAL GRADE 2,4 (80%)- AND 2,6 (20%)- TOLUENE DIISOCYANATE

(CAS NO. 26471-62-5)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT
ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF COMMERCIAL GRADE 2,4 (80%)- AND 2,6 (20%)- TOLUENE DIISOCYANATE

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IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park
North Carolina 27709

August 1986

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTE TO THE READER

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

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

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

Special Note: This Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee on September 22, 1982 [see pages 11 and 12]. Thereafter, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis Studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix M.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. The categories of evidence of carcinogenicity adopted by the NTP in June 1983 were not used to evaluate these data. This final Technical Report supercedes all previous drafts of this report that have been distributed.

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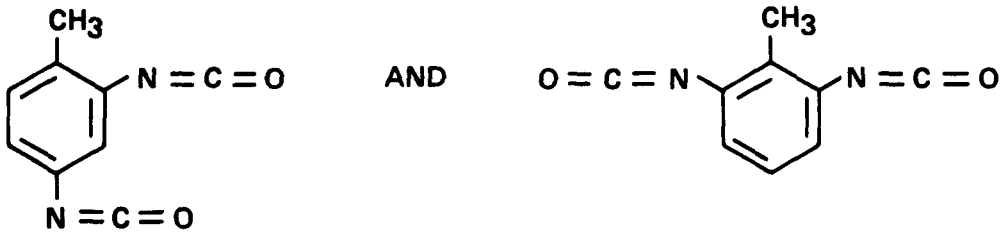
MIXTURE OF



2,4- (80%) AND 2,6- (20%)

TOLUENE DIISOCYANATE

CAS NO. 26471-62-5

ABSTRACT

Groups of 50 female F344/N rats and 50 female B6C3F$_1$ mice were administered commercial grade toluene diisocyanate (80% 2,4- and 20% 2,6-) in corn oil by gavage at doses of 60 or 120 mg/kg body weight, 5 days per week for 105 or 106 weeks. Groups of 50 male F344/N rats received 30 or 60 mg/kg and groups of 50 male B6C3F$_1$ mice received 120 or 240 mg/kg on the same schedule. Dosage analyses of toluene diisocyanate indicated that the chemical had reacted in the corn oil vehicle, resulting in actual gavage concentrations 77% to 90% of theoretical values. Groups of 50 rats and 50 mice of each sex received corn oil only and served as vehicle controls.

Survival in all groups of dosed rats in the 2-year studies was shorter ($P \leq 0.005$) than that of the controls; depressions in mean body weight gain relative to controls were greater than 10% in all dosed rat groups throughout most of the study. A dose-dependent pattern of cumulative toxicity began at 70 weeks and culminated in excessive mortality, indicating the estimated maximum tolerated dose had been exceeded for rats. Acute bronchopneumonia occurred at increased incidences in groups of dosed male and female rats (males: control, 2/50; low dose, 6/50; high dose, 14/50; females: 1/50, 10/50, 25/49).

Subcutaneous tissue fibromas or fibrosarcomas (combined) in male rats occurred with a positive trend ($P < 0.01$; 3/50, 6/50, 12/50). The incidence in the high dose group was higher than that in the controls ($P \leq 0.01$). The same tumor comparisons were significant ($P < 0.001$) in female rats by the life table analysis. Mammary gland fibroadenomas in female rats occurred with a positive trend ($P < 0.001$), and the incidences in low and high dose groups were significantly higher than that in controls ($P \leq 0.01$).

Pancreatic acinar cell adenomas in male rats occurred with a positive trend ($P < 0.05$; 1/47, 3/47, 7/49). The incidence in the high dose group was higher than that in the controls ($P < 0.05$).

The incidences of pancreatic islet cell adenomas in female rats were higher by the incidental tumor test ($P \leq 0.01$) in low dose (6/49) and high dose (2/47) groups than in controls (0/50). An islet cell carcinoma was also observed in a low dose female rat. The incidences of female rats with neoplastic nodules in the liver occurred with a positive trend ($P < 0.05$; 3/50, 8/50, 8/48), and the incidence in the high dose group was higher ($P < 0.05$) than that in the controls.

Survival of high dose male mice in the 2-year study was significantly shorter than that of the controls ($P < 0.001$). During the second year of the study, mean body weight gains of high dose male mice were less than those of the controls. Cytomegaly of kidney tubular epithelium was found in 45/48 (94%) low dose male mice and 41/50 (82%) high dose male mice but not in any of the controls.

Hemangiomas or hemangiosarcomas (combined) of the circulatory system in female mice occurred with a positive trend ($P \leq 0.01$; control, 0/50; low dose, 1/50; high dose, 5/50). The incidence in the high dose group was significantly higher than that in the controls ($P < 0.05$).

Hepatocellular adenomas in female mice occurred with a positive trend ($P \leq 0.001$; 2/50, 3/50, 12/50), and the incidence in the high dose group was higher than that in the controls ($P < 0.01$).

Toluene diisocyanate was mutagenic in *Salmonella typhimurium* strains TA98 and TA100 in the presence (but not the absence) of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9; it was not mutagenic in strains TA 1535 or 1537.

An audit of the experimental data for these 2-year toxicological and carcinogenicity studies on commercial grade 2,4- and 2,6-toluene diisocyanate was conducted. There were no data discrepancies that influenced the final interpretations.

Under the conditions of these gavage studies, commercial grade toluene diisocyanate in corn oil was carcinogenic for F344/N rats, causing subcutaneous fibromas and fibrosarcomas (combined) in males and females, pancreatic acinar cell adenomas in males, and pancreatic islet cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in females. Toluene diisocyanate was not carcinogenic for male $B6C3F_1$ mice. TDI was carcinogenic for female $B6C3F_1$ mice, causing hemangiomas or hemangiosarcomas (combined), as well as hepatocellular adenomas.

CONTRIBUTORS

These carcinogenesis studies of toluene diisocyanate were conducted at Litton Bionetics, Inc. under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year studies for F344 N rats and $B6C3F_1$ mice were begun in December 1978 and completed in January 1981.

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SUMMARY OF PEER REVIEW COMMENTS ON THE CARCINOGENESIS STUDIES OF COMMERCIAL GRADE TOLUENE DIISOCYANATE

On 22 September 1982 this technical report on the carcinogenesis studies of commercial grade toluene diisocyanate underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. This public review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The following precis represents the critiques made by the principal reviewers, as well as comments from and discussion by the Peer Review Panel, NTP staff, and attendees.

Dr. Elashoff, a principal reviewer, agreed with the conclusions. He noted that due to the common lethal nontumorigenic toxicity, the life table and incidental tumor tests were the appropriate statistical analyses. As a second principal reviewer, Dr. Mirer said the conclusions were appropriate. He criticized the storage of gavage solutions at room temperature in view of the reactivity of TDI with corn oil. He said the compound and dose related toxicity indicated the doses may have been too high in rats yet this did not compromise the conclusions.

As a third principal reviewer, Dr. Holland accepted the report as written. He commented that the interpretation of these studies was complicated by the instability of the material in contact with water, as would occur in the gastrointestinal tract. However, since similar degradation would occur if exposure were by the respiratory route, the data were, in his opinion, a valid representation of TDI tumorigenicity. Dr. M. Dieter, NTP, said the corn oil was not anhydrous or kept in a desiccator, and degradation rates of TDI would be given in the report.

In discussion from the floor, Dr. L. Rampy, Dow Chemical Company and representing the International Isocyanate Institute, reiterated and added to comments sent to the review panel and NTP staff prior to the meeting. First, since the occupational route of exposure to TDI was mainly inhalation, he said the gavage route was improper because toxicity, spectrum of metabolites, and other factors would likely differ between the routes. He opined that TDI would be converted after oral dosing to toluene diamine, a known animal carcinogen. He requested that the report be deferred.

Dr. Swenberg stated the study should have been stopped at one year due to excessive mortality and chemically associated toxicity. He said that bronchial pneumonia may have been a cause of the animals dying early. Dr. Holland said the effect of reducing a sample size in a positive study is of less overall concern than the effect of reducing sample size in the case of a negative study. Dr. Elashoff noted that, in the case of TDI, despite reduction of power and sensitivity due to early mortality, the tumorigenic effects were such that there was significance both in trend tests and pairwise comparisons at a number of target sites.

Dr. Scala requested that statements be added about exceeding the maximum tolerated dose in rats, and possibly in male mice. Dr. Mirer asked that there be in the abstract a comment about the reactivity of TDI with corn oil.

Dr. Elashoff moved that the report on the carcinogenesis studies of toluene diisocyanate be accepted conditional on the revisions, written and discussed. Dr. Holland seconded the motion and the technical report was approved by the Peer Review Panel (nine affirmative votes and one abstention; Dr. Schwetz).

I. INTRODUCTION

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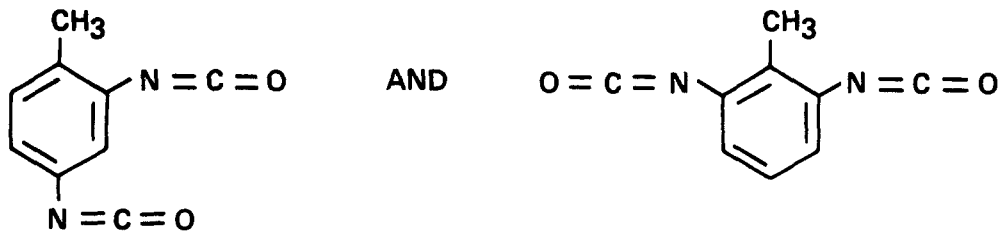
MIXTURE OF



2,4-
(80%)

2,6-
(20%)

TOLUENE DIISOCYANATE

CAS NO. 26471-62-5

Toluene diisocyanate (TDI) is commercially produced as an approximate 80:20 mixture of the 2,4-and 2,6-isomers. In 1980, 580,000 pounds of this chemical were produced in the United States, primarily for use in the manufacture of flexible polyurethane foams (USITC, 1981). These foam elastomers are found in furniture and automobile cushions, carpet underlays, pillow filling, mattresses, insulation, shoes, purses, and toys (Kirk-Othmer, 1970). TDI is also used to produce polyurethane coatings for lacquers and wood finishes (IARC, 1979).

TDI reacts readily with polyols, water, urea, urethanes, amines, and other basic compounds (E.I. DuPont, 1969; Ehrlicher, 1974). Concentrations as high as 10 ppm TDI have been measured in the air above urethane foams during their production (Buist, 1970). The maximum allowable 8-hour time weighted average concentration of 2,4-toluene diisocyanate to which workers can be exposed is 0.02 ppm (U.S. CFR, 1974).

The oral LD50 value for TDI in rats is 5.8 g/kg body weight (Zapp, 1957), and the LC50 values for rats and mice are 14 and 10 ppm, respectively (Duncan, 1962).

Skin, eye, and respiratory tract irritation has been reported in both humans and rats exposed to TDI in air (Union Carbide, 1976; Patty, 1963). Hypersensitivity to TDI, manifested as an asthma-like response, has been reported in workers exposed to the chemical (Parkes, 1970; Taylor, 1970; Sangha and Alarie, 1979), and a 10-hour TWA exposure concentration of 5 ppb TDI has been recommended for workplace air (NIOSH, 1979).

Toluene 2,6-diisocyanate (2,6-TDI) is unstable in hydroxylic solvents and reacts even more rapidly with primary and secondary amines. At very low concentrations in water, it hydrolyzes stepwise to first form 2-amino-6-isocyanatotoluene, then 2,6-diaminotoluene. At higher concentrations, poly-ureas are formed by the reaction of amino groups of the hydrolysis products with the isocyanate. In an aqueous suspension of stomach contents the half-life of 2,6-TDI was less than 2 minutes. The half-life of 2,6-TDI in serum was less than 30 seconds (RTI, 1985).

When 2,6-TDI was given orally to 11 adult male Fischer 344 rats in corn oil, most of the 2,6-TDI formed polymers in the gastrointestinal tract (RTI, 1985). At doses of 900 mg/kg body weight, the 2,6-TDI usually polymerized and lined the stomach, slowing or preventing the migration of food into the intestines. In these cases, the stomachs became greatly distended. At doses of 60 mg/kg body weight, these results were not observed.

Most 2,6-TDI-derived materials were excreted in feces or were found in the gastrointestinal tract 72 hours after dosing. Excretion in breath was insignificant. Approximately 2.5 times as much 2,6-TDI-derived materials were excreted in urine after a 60 mg/kg oral dose (12%) than after a 900 mg/kg dose (5%). More than half of the xenobiotic related material excreted in urine was 2,6-bis(acetylamino)toluene. Increased urinary excretion of metabolites of 2,6-TDI with decreasing dosage is consistent with the lower concentration of 2,6-TDI in the stomach permitting increasing amounts of the 2,6-TDI to be hydrolyzed completely to monomeric 2,6-diaminotoluene rather than forming polymers. The 2,6-diaminotoluene could then be absorbed, acetylated, and excreted in urine. 2,6-TDI-derived materials were not concentrated in any tissues (RTI, 1985).

Both 2,4- and 2,6-diaminotoluene were mutagenic in *Salmonella typhimurium* TA1538 (Dybing and Thorgeirsson, 1977; Andersen et al., 1980). Although 2,4-toluene diisocyanate was reported as not mutagenic in *S. typhimurium* TA1535, TA1538, TA98, and TA100, with or without metabolic activation with S-9 preparation from Aroclor 1254-induced Sprague-Dawley rats (Anderson and Styles, 1978), an 80:20 mixture of 2,4- and 2,6-toluene diisocyanate was mutagenic in a narrow dose range in *S. typhimurium* TA100, TA98, and TA1538 after metabolic activation with rat liver S-9 preparation from phenobarbital-induced rats (Andersen et al., 1980). Differences in the results from the two studies are probably due to differences in the test conditions. Using the micronucleus mutagenesis test procedure, Loeser (1983) observed no mutagenic responses in groups of five male or female Sprague-Dawley rats or CD-1 mice exposed to TDI vapors at doses of 0, 0.05, or 0.15 ppm (v/v) 6 hr/day, 5 days/wk for 4 weeks.

Both 2,6-TDI and a mixture of 2,4- and 2,6-TDI were mutagenic in *Salmonella typhimurium* strains TA98 and TA100 in the presence but not the absence of metabolic activation provided by 9000 × g liver supernatant (S-9) fractions from Aroclor 1254-induced male Sprague-Dawley rats or Syrian golden hamsters (Appendix L). Toluene diisocyanate was not mutagenic in *S. typhimurium* strains TA1535 or TA1537 with or without metabolic activation.

No evidence of 2,4-/2,6-TDI (80/20)-associated benign or malignant lesions was reported by Loeser (1983) following vapor exposure of male and female Sprague-Dawley rats and CD-1 mice to 0, 0.05, or 0.15 ppm (6 hr/day, 5 days/wk) for approximately two years.

A commercial TDI mixture was tested since a large number of workers (approximately 40,000) are potentially exposed to these isomers and because no long-term studies were available.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

DOSE PREPARATION

SHORT-TERM STUDIES

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Data Recording and Statistical Methods

CHEMICAL ANALYSES

Toluene diisocyanate (Hylene®) was obtained in two lots from E.I. duPont de Nemours and Co. (Wilmington, DE). Lot no. 228 was used for the single-dose, 14-day, and 13-week studies and for the first 14 months of the 2-year studies. Lot no. 414417 was obtained to complete the 2-year studies.

Purity and identity analyses were conducted on both lots at Midwest Research Institute (Appendix G). The results of elemental analyses of lot 228 for carbon, hydrogen, and nitrogen and of lot 414417 for carbon and hydrogen agreed with the theoretical values. The results for nitrogen in lot 414417 were slightly high. When both lots were analyzed in comparable systems by vapor-phase chromatography, lot 228 was found to contain six trace impurities, each with an area of less than 0.02% of the major peak, while lot 414417 contained only two of these impurities (both totalling 0.2% of the major peak). Lot 414417 still exhibited only two impurities when analyzed in a second system. The infrared, ultraviolet, and nuclear magnetic resonance spectra for both lots were consistent with the literature spectra and with each other. Comparison of the integration ratios of the nuclear magnetic resonance for the protons on the 2,4- and 2,6-isomers indicated that lot 228 consisted of approximately 80% of the 2,4- and 20% of the 2,6-isomers, and lot 41447 was approximately 85% of the 2,4- and 15% of the 2,6-isomers.

As a part of the initial stability analysis of gavage solutions, Midwest Research Institute determined that TDI reacted very rapidly with water — approximately 20% remained less than 15 minutes after the aqueous solution was prepared (MRI Report, August 7, 1975). Campbell et al., (1975 and 1976) have reported that, upon reaction with water, TDI forms a disubstituted urea, N,N'-bis(3-isocyanato-4-methylphenyl) urea (Figure 1). This material is insoluble in TDI and precipitates, thereby inhibiting further reaction to form polymers (Figure 2). If TDI is warmed to increase the solubility of this disubstituted urea, the relative amount of the polymers can be increased. It was therefore important that TDI be stored in a dry environment.

Lot 228 was initially received at the bioassay laboratory in two 10-pound metal cans. Storage conditions were varied over the course of its use in an attempt to determine the most suitable conditions. These storage conditions may have contributed to the cloudy appearance in the first can. The cloudiness was first noticed in March 1979 (the 2-year studies began in December 1978), and the testing laboratory was directed to use the second can. Use of the second can began in July 1979, and this too was found to be cloudy. Analysis of this material by Midwest Research Institute (Appendix H) indicated that the sample contained approximately 0.5% (w/w) of a nonvolatile material dissolved in the bulk liquid.

The isolated dried precipitate was analyzed by mass spectrometry and was determined to be the urea (Figure 1) and its polymeric analogs (Figure 2). Quantitation of the precipitated material indicated that there was 0.3% (w/w) of this precipitate suspended in the bulk liquid. Since these materials may be formed once the TDI reaches the stomach of the animal, this small amount was

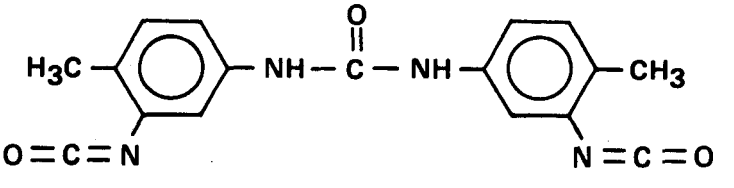


Figure 1. Structure of N,N'-Bis(3-isocyanato-4-methylphenyl)Urea

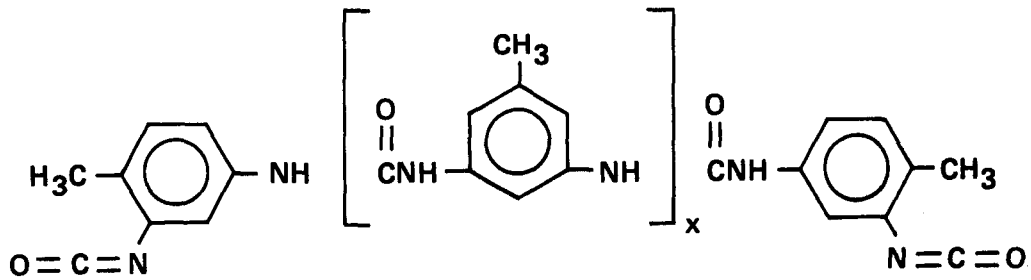


Figure 2. Polymeric Analog of N,N'-Bis(3-isocyanato-4-methylphenyl)Urea

not considered to be a serious problem. However, a new lot of the chemical (414417) was procured and placed on test after being analyzed and found to be suitable (May 1980). No evidence of any polymer was detected in this lot over the 10-month period that it was used and stored in a desiccator at the testing laboratory. Analysis by infrared spectrometry and vapor-phase chromatography (using the same system used for lot 228) indicated no change in the purity of the bulk chemical liquid, despite the presence of the precipitate in lot 228.

DOSE PREPARATION

TDI was administered by gavage because the chemical is unstable in water or in feed. Doses were prepared by weighing appropriate amounts of TDI and mixing them with enough corn oil of normal moisture content (0.05%) to give the desired concentrations. (The stability of TDI in corn oil and the results of analysis of the corn oil for moisture are presented in Appendixes I and J.) All glassware was oven dried and stored in a dessicator until used. Gavage solutions were stored at room temperature outside of a desiccator.

The concentration of TDI in the corn oil formulations was analyzed periodically at the bioassay laboratory (Appendix K). Since TDI corn oil formulations were used for no more than 7 days, only those analyses performed during this time period are presented in Table K1. According to the MRI report (Appendix I), the animals could have received 77-90% of the target dose at the end of the dosing period (7 days after preparation). The results from the bioassay laboratory indicate the importance of glassware preparation and sample handling, since the results did not always parallel those predicted by the MRI stability study.

On the average, the groups of animals that received 9, 18, 36, or 72 mg/ml formulations received approximately 77%, 82%, 90%, or 84% of the target doses, respectively. When doses in the 2-year study are examined in terms of the milligrams of TDI administered per kilogram of body weight, the following estimated doses can be calculated:

	Rats				Mice			
	Males		Females		Males		Females	
Target dose (mg/kg)	30	60	60	120	120	240	60	120
Estimated dose (mg/kg)	23	49	49	108	108	202	49	108

II. MATERIALS AND METHODS: SINGLE-DOSE STUDIES

SINGLE-DOSE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice (C57BL/6N×C3H/HeN MTV-) were obtained from Frederick Cancer Research Center, quarantined, and held for approximately 6 weeks before the test began. Animals were approximately 10 weeks old when placed on study.

Groups of five rats of each sex were administered a single dose of TDI (2,150, 3,160, 4,640, 6,810, 10,000, or 14,700 mg/kg body weight) in corn oil by gavage, and groups of five mice of each sex received doses of 2,150 (males only), 3,160, 4,640, 6,810, or 10,000 mg/kg by the same route. No controls were used. All animals were observed for mortality for 14 days; observations were made every 30 minutes for the first 8 hours and then daily for the rest of the study.

Rats were housed two or three per cage and mice were housed five per cage. Animals received water and feed *ad libitum* during the observation period. Details of animal maintenance are presented in Table 1. Necropsies were performed on all animals.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and held for 2 to 3 weeks before the study began. Animals were 6 to 7 weeks old when placed on study.

Two studies were conducted. In the first, groups of five rats and mice of each sex were administered TDI in corn oil at doses of 0, 500, 1,000, 2,000, 3,000, or 4,000 mg/kg for 14 consecutive days. Similar groups of rats and mice in the second study received doses of 0, 30, 60, 120, 240, or 500 mg/kg on the same schedule.

Rats were housed two to three per cage and mice five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 1.

Rats and mice were observed daily for mortality and were weighed on days 0, 7, and 14. Necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Two 13-week studies were conducted to evaluate the cumulative toxicity of TDI and to determine the doses to be used in the 2-year studies.

Three-to-four-week-old male and female F344 rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center for the first study and from Charles River Breeding Laboratories for the second study. Animals on the first study were held for 12 days, randomized by weight, and then assigned to test groups so that average cage weights were approximately equal for all animals of the same sex and species. Rats were 6 weeks old and mice 5 weeks old when placed on study. For the second study, rats were held 8 weeks and mice 5 weeks before the test began; the animals were 12 and 9 weeks old, respectively, when placed on study.

Rats and mice were housed five per cage in polycarbonate cages (Table 1). They received Purina® Lab meal and water in bottles (acidified to pH 2.5 for bacterial control) *ad libitum*.

In the first study, groups of 10 rats of each sex received TDI in corn oil by gavage at doses of 0, 7, 15, 30, 60, 120, or 240 mg/kg body weight, 5 days per week for 13 weeks, and groups of 10 mice of each sex received doses of 0, 6, 12, 25, 50, or 100 mg/kg on the same schedule. Rats and mice in the second study were administered TDI at doses of 0, 15, 30, 60, 120, or 240 mg/kg.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue

masses or swelling. Body weight data were collected weekly.

At the end of the 91-day study, survivors were killed, and necropsies were performed on animals that survived to the end of the study and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group. The following specimens were examined histopathologically for control and high dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats received TDI in corn oil by gavage at doses of 0, 30, or 60 mg/kg body weight; groups of 50 male mice received 0, 120, or 240 mg/kg; groups of 50 female rats and 50 female mice received 0, 60, or 120 mg/kg. Doses were administered 5 days per week for 106 weeks (rats) or 105 weeks (mice).

Additional groups of 50 rats and 50 mice of each sex were started as untreated controls but were subsequently sacrificed at 87 weeks.

Source and Specifications of Test Animals

Six-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries, observed for 6 weeks, and then assigned to cages according to a table of random numbers. The cages were then assigned to control and dosed groups according to another table of random numbers. Rats and mice were 12 weeks old when placed on study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages covered with nonwoven filter sheets (Table 1). Racks and filters were changed once every 2 weeks. Cages, bedding, and glass water bottles (equipped with stainless steel sipper tubes) were replaced twice per week. Tap water (acidified to pH 2.5 for bacterial control) and feed were available *ad libitum*.

The temperature in the animal rooms was 20°-26°C and the humidity was 20%-78%. Twelve to 15 changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Clinical Examinations and Pathology

All animals were observed twice daily for mortality and morbidity. Clinical signs and the results of palpations were recorded every 4 weeks. Body weights were recorded once per week for the first 13 weeks and then monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the study were killed with carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The classification of neoplastic nodules was done according to the recommendations of Squire and Levitt (1975) and the National Academy of Sciences (1980).

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissues were verified, and histotechniques were evaluated. All tumor diagnoses, target tissues, and tissues from a randomly selected 10% of the animals were evaluated by a pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative slides selected by the Chairperson were reviewed blindly by PWG pathologists, who reached a consensus and compared their findings with the original diagnoses. When disagreements occurred, the PWG sent the appropriate slides and their comments to the original pathologist for review. (This procedure has been described by Maronpot and Boorman, 1982.) The final diagnosis represents a consensus of contractor pathologists and the NTP Pathology Working Group.

Data Recording and Statistical Methods

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

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. All animals dying of accidents or found to be missing were statistically censored from the survival analysis at the time of death. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. All reported P values for the survival analysis are two-sided.

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

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

The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel methods to obtain an overall P-value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975).

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time

intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually necropsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

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

For studies in which there is little effect of compound administration on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Rats: males and females—2,150, 3,160, 4,640, 6,810, 10,000 or 14,700 mg/kg body weight toluene diisocyanate in corn oil	Rats: 1st study: 0, 500, 1,000, 2,000, 3,000, or 4,000 mg/kg; 2nd study: 0, 30, 60, 120, 240, or 500 mg/kg body weight toluene diisocyanate in corn oil	Rats: males and females—1st study: 0, 7, 15, 30, 60, 120, or 240 mg/kg body weight toluene diisocyanate in corn oil; 2nd study: 0, 15, 30, 60, 120, or 240 mg/kg body weight toluene diisocyanate in corn oil	Rats: males: 0, 30, or 60 mg/kg body weight; females: 0, 60, or 120 mg/kg body weight toluene diisocyanate in corn oil
	Mice: males: 2,150, 3,160, 4,640, 6,810, or 10,000 mg/kg; females: 3,160, 4,640, 6,810, or 10,000 mg/kg body weight toluene diisocyanate in corn oil	Mice: 1st study: 0, 500, 1,000, 2,000, 3,000, or 4,000 mg/kg toluene diisocyanate in corn oil; 2nd study: 0, 30, 60, 120, 240, or 500 mg/kg	Mice: males and females—1st study: 0, 6, 12, 25, 50, or 100 mg/kg body weight toluene diisocyanate in corn oil; 2nd study: 0, 15, 30, 60, 120, or 240 mg/kg body weight TDI in corn oil.	Mice: males: 0, 120 or 240 mg/kg body weight; females: 0, 60, or 120 mg/kg body weight toluene diisocyanate in corn oil.
Duration of Dosing	Single dose	Daily for 14 days	Five days per week for 13 weeks	Five days per week for 106 weeks (rats) or 105 weeks (mice)
Type and Frequency of Observation	Observed for mortality every 1/2 hour for first 8 hrs and then daily	Observed daily for mortality and morbidity	Observed twice daily for mortality and morbidity; weighed weekly	Observed twice daily for mortality and morbidity; clinical signs taken and palpation done every 4 weeks; weighed once per week for 13 weeks, then monthly
Necropsy and Histologic Examination	Necropsies were performed on all animals	Necropsies were performed on all animals	Necropsies were performed on all animals; histopathologic examinations performed on control and high-dose groups	Necropsies and histopathologic examinations were performed on all animals

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Animals and Animal Maintenance				
Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Frederick Cancer Research Center (Frederick MD)	Frederick Cancer Research Center	1st study: Frederick Cancer Research Center 2nd study: Charles River Breeding Laboratories (Wilmington, DE)	Harlan Industries, Inc. (Indianapolis, IN)
Time Held Before Start of Test	6 weeks	1st study: 3 weeks 2nd study: 2 weeks	1st study: 12 days 2nd study: rats: 8 weeks; mice: 5 weeks	Rats: 6 weeks Mice: 6 weeks
Age When Placed on Study	10 weeks	1st study: 7 weeks 2nd study: 6 weeks	1st study: rats: 6 weeks; mice: 5 weeks 2nd study: rats: 12 weeks mice: 9 weeks	Rats: 12 weeks Mice: 12 weeks
Age When Killed	12 weeks	1st study: 9 weeks 2nd study: 8 weeks	1st study: rats: 19 weeks mice: 18 weeks 2nd study: rats: 25 weeks mice: 22 weeks	119 weeks
Method of Animal Distribution			Animals were randomized by weight	Animals assigned to groups according to a series of computer-generated random numbers
Feed	Purina® Laboratory Chow (ground), Ralston Purina Co. (St. Louis, MO); provided *ad libitum*	Same as single-dose study	Same as single-dose study	Same as single-dose study but supplied pellets
Bedding	Ab-sorb-dri® hard-wood chips Lab Products, Inc (Garfield, NJ)	Same as single-dose study	Same as single-dose study	Same as single-dose study
Water	Tab water acidified to pH 2.5 provided by water bottles *ad libitum*	Same as single-dose study	Same as single-dose study	Same as single dose study

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Studies	14-Day Studies	13-Week Studies	2-Year Studies
Animals and Animal Maintenance				
Cages	Polycarbonate (Lab Products, Inc. Garfield, NJ)	Polycarbonate	Polycarbonate	Polycarbonate
Cage Filters	-	-	Non-woven polyester	Non-woven polyester filter paper, Snow Filtration Co. (Cincinnati, OH)
Animals Per Cage	Rats: 2-3 per cage; Mice: 5 per cage	Rats: 2-3 per cage; Mice: 5 per cage	5 per cage	5 per cage
Animal-Room Environment	—	—	22° to 25°C; 30%-70% relative humidity	20° to 26°C; 20%-78% relative humidity; 12-15 room air changes per hour; 12 hours per day fluorescent light
Other Chemicals on Test in Same Room	Rats: diallyl phthalate, 2,6-dichloro-p-phenylenediamine, caprolactam; Mice: diallyl phthalate, 2,6-dichloro-p-phenylene-diamine, caprolactam	Diphenyl methane diisocyanate	None	None
Chemical/Vehicle Mixture				
Preparation	Toluene diisocyanate was dissolved in corn oil at a concentration of 500 mg/ml	Toluene diisocyanate was dissolved in corn oil at a concentration of 250 mg/ml for the 1st study and 45 mg/ml for the 2nd study	Toluene diisocyanate was dissolved in corn oil at concentrations of 16 or 32 mg/ml	Toluene diisocyanate was dissolved in corn oil at concentrations of 9, 18, 36, or 72 mg/ml
Maximum Storage Time	Prepared within 2 hours of dosing	Prepared within 2 hours of dosing	Prepared daily	1 week
Storage Conditions	-	-	-	Room temperature

III. RESULTS

RATS

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-DOSE STUDIES

Mortality was proportional to the dose of TDI administered (Table 2). Loss in mean body weight was greater than 10 g in all groups of dosed males. In rats receiving 10,000 or 14,700 mg/kg, death was preceded by labored breathing, inactivity, and diarrhea. White, crystalline material was found in the stomach and dark red lungs were observed at necropsy; these findings were dose related.

FOURTEEN-DAY STUDIES

Two 14-day studies were conducted because the initial study resulted in excessive mortality in all dosed groups (Table 3). Dose levels for the second 14-day study were an order of magnitude less than those in the original study; few animals died and deaths were not dose related. Mean body weight relative to controls was depressed by more than 10% in male rats administered doses of 120 mg/kg or more and female rats administered 500 mg/kg.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED A SINGLE DOSE OF TOLUENE DIISOCYANATE IN CORN OIL BY GAVAGE

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weights (grams)		
		Initial	Final	Change
MALES				
2,150	3/5 (5,9)	272	260	-12
3,160	2/5 (1,3,14)	264	244	-20
4,640	3/5 (2,10)	238	214	-24
6,810	3/5 (4,5)	222	204	-18
10,000	0/5 (1,1,1,2,2)	263	—	—
14,700	0/5 (2,2,2,2,2)	241	—	—
FEMALES				
2,150	5/5	162	165	+ 3
3,160	3/5 (3,3)	163	161	- 2
4,640	3/5 (2,2)	150	144	- 6
6,810	0/5 (2,2,3,4,4)	150	—	—
10,000	1/5 (3,3,3,3)	157	133	-24
14,700	0/5 (1,2,2,2,2)	144	—	—

(a) Number surviving/number per group

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED TOLUENE DIISOCYANATE IN CORN OIL BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
		FIRST STUDY			
MALES					
0	4 5 (11)	120	174	+54	—
500	2 5 (1,2,9)	119	131	+12	-25
1,000	1 5 (1,1,7,10)	120	164	+44	- 6
2,000	0 5 (2,2,3,3,5)	120	—	—	—
3,000	0 5 (2,3,4,6,6)	119	—	—	—
4,000	0 5 (2,2,3,3,4)	119	—	—	—
FEMALES					
0	5 5	99	126	+27	—
500	3 5 (8,9)	99	111	+12	-12
1,000	1 5 (2,6,6,9)	98	98	0	-22
2,000	1 5 (2,2,2,3)	99	100	+ 1	-21
3,000	0 5 (2,2,4,5,6)	99	—	—	—
4,000	0 5 (3,3,3,4,6)	99	—	—	—
		SECOND STUDY			
MALES					
0	5 5	97	163	+66	—
30	4/5 (10)	97	158	+61	- 3
60	5/5	97	156	+59	- 4
120	5/5	98	144	+46	-12
240	4/5 (5)	97	126	+29	-23
500	5/5	97	106	+ 9	-35
FEMALES					
0	5/5	87	126	+39	—
30	4/5 (3)	87	125	+38	- 1
60	5/5	87	119	+32	- 6
120	5/5	87	119	+32	- 6
240	4/5 (7)	87	120	+33	- 5
500	4/5 (4)	86	105	+19	-17

(a) Number surviving/number per group

(b) Weight of the dosed group relative to that of the controls =

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

III. RESULTS: RATS—THIRTEEN-WEEK STUDIES

THIRTEEN-WEEK STUDIES

Two 13-week studies were conducted. In the initial study, additional groups were started at doses of 0, 120, and 240 mg/kg when no weight gain depression was observed in the original test groups after 60 days on study (Table 4). Since the patterns of mortality between the two 120 mg/kg groups were inconsistent and there was no dose-response relationship when 240 mg/kg was administered, the second 13-week study was conducted.

In the second study, only one death (a female receiving 240 mg/kg) was considered to be compound related (Table 4). Mean body weight, relative to controls, was depressed by 10% or more in male rats receiving 120 or 240 mg/kg; weight gain was not depressed in female rats. Mucoid bronchopneumonia was mild to moderate in 8/10 males that received 240 mg/kg, moderate to severe in 2/10 females administered 240 mg/kg, and moderate in 1/2 males that received 120 mg/kg and died before the end of the study. The accumulation of mucoid material in bronchioles was referred to as "mucoid bronchopneumonia," even though this lesion was not entirely inflammatory. The less severe lesions consisted of mucoid material and a few plump macrophages that were assumed to have originated as alveolar macrophages. The more pronounced lesions had more neutrophils.

Doses of 30 and 60 mg/kg were selected for males and doses of 60 and 120 mg/kg were selected for females in the 2-year study because depression in mean body weight gain and mucoid bronchopneumonia had been observed at higher doses.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed rats were lower than those for the controls after week 10 in males and week 20 in females. The depressions in mean body weight gains were dose related (Table 5 and Figure 3). No other compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival of male and female rats administered TDI in corn oil at the doses used in these studies, and those of the controls, are shown by the Kaplan and Meier curves in Figure 4. In male rats, the survival of animals in the two dosed groups was significantly shorter than that of the controls ($P<0.001$). In females, the survival in each dosed group was significantly shorter than that in the controls (high dose, $P<0.001$; low dose, $P=0.005$), and the survival in the high dose group was significantly shorter than that in the low dose group ($P=0.001$). One control, six low dose, and three high dose males and one high dose female and five low dose females were accidentally killed and were censored from the statistical analysis of survival.

In male rats, 36/50 (72%) of the controls, 14/50 (28%) of the low dose, and 8/50 (16%) of the high dose group lived to the end of the study at 108 weeks. In female rats, 36/50 (72%) of the controls, 19/50 (38%) of the low dose, and 6/50 (12%) of the high dose group lived to the end of the study at 108 weeks. The survival data included one control male and one high dose female that died during the termination period of the study. For statistical purposes, these animals are considered to have been killed at the end of the study. Because of the reduced survival in dosed male and female rats, the statistical procedures that adjust for intercurrent mortality (life table and incidental tumor tests) were regarded as more meaningful than the "unadjusted" analyses in the evaluation of tumor incidence data in these groups.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED TOLUENE DIISOCYANATE IN CORN OIL BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)* (Week of Death)	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(b)* (Percent)
		Initial	Final *(d)*	Change	
FIRST STUDY					
MALES					
0	10/10	110	288	+178	—
7	9/10 (8)	111	283	+172	- 2
15	10/10	112	284	+172	- 1
30	7/10 (1,2,7)	112	277	+165	- 4
60	8/10 (6,6)	108	270	+162	- 6
120	7/10 (6,6,7)	109	249	+140	-14
0 *(c)*	10/10	99	288	+189	—
120 *(c)*	9/10 (12)	99	276	+177	- 4
240 *(c)*	7/10 (10,13,13)	99	237	+138	-18
FEMALES					
0	10/10	96	190	+ 94	—
7	9/10 (7)	95	190	+ 95	0
15	9/10 (7)	96	184	+ 88	- 3
30	7/10 (1,1,5)	95	181	+ 86	- 5
60	7/10 (2,5,5)	96	177	+ 81	- 7
120	6/10 (1,1,6,6)	96	172	+ 76	- 9
0 *(c)*	10/10	81	185	+104	—
120 *(c)*	10/10	82	175	+ 93	- 5
240 *(c)*	10/10	81	155	+ 74	-16
SECOND STUDY					
MALES					
0	10/10	189	317	+128	—
15	10/10	178	315	+137	- 1
30	10/10	185	316	+131	0
60	9/10 (7)	172	312	+140	- 2
120	8/10 (8,9)	177	283	+106	-11
240	10/10	182	278	+ 92	-12
FEMALES					
0	10/10	150	198	+ 48	—
15	10/10	144	193	+ 49	- 3
30	10/10	147	193	+ 46	- 3
60	10/10	148	198	+ 50	0
120	10/10	149	192	+ 43	- 3
240	9/10 (7)	152	189	+ 37	- 5

(a) Number surviving number per group

(b) Weight of the dosed group relative to that of the controls =

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

(c) Started 2 months after other group

(d) Weight at day 84

TABLE 5. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF TOLUENE DIISOCYANATE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh controls)	High Dose No. of Survivors
MALE								
0	184	50	182	99	50	198	108	50
1	200	50	190	95	50	200	100	50
2	211	50	210	100	50	212	100	50
3	224	50	227	101	50	228	102	49
4	240	50	240	100	50	239	100	48
5	232	50	238	103	48	237	102	48
6	253	50	249	98	48	256	101	47
7	262	50	260	99	47	268	102	47
8	272	50	263	97	45	266	98	45
9	288	50	277	96	44	276	96	44
10	283	50	268	95	43	266	94	43
11	296	50	280	95	41	266	90	42
12	297	50	284	96	41	272	92	40
13	302	50	290	96	41	278	92	40
16	323	50	306	95	41	294	91	39
20	353	50	338	96	41	309	88	39
24	357	49	338	95	41	323	90	39
28	371	49	351	95	39	330	89	36
32	384	49	366	95	39	341	89	36
36	396	49	367	93	39	338	85	36
40	402	49	378	94	37	341	85	35
44	411	49	378	92	37	339	82	33
48	418	49	387	93	37	343	82	32
52	418	49	385	92	35	337	81	32
56	426	49	386	91	33	335	79	30
60	421	49	379	90	33	325	77	29
64	429	49	386	90	33	332	77	29
68	425	49	382	90	31	324	76	29
72	427	49	376	88	31	324	76	27
76	430	48	377	88	30	325	76	25
80	425	47	370	87	28	329	77	23
84	424	47	370	87	27	327	77	20
88	410	46	354	86	27	323	79	20
92	412	45	358	88	26	314	77	16
96	412	42	365	89	22	316	77	14
100	407	39	358	87	20	309	75	13
104	403	36	350	86	18	318	78	10
FEMALE								
0	130	50	134	103	50	139	107	50
1	137	50	138	101	50	145	106	50
2	146	50	145	99	50	149	102	50
3	154	50	151	98	50	156	101	50
4	161	50	157	98	50	162	101	50
5	161	50	161	100	48	166	103	50
6	167	50	166	99	47	166	99	50
7	171	50	171	100	46	173	101	50
8	174	50	172	99	44	173	99	49
9	178	50	178	100	43	182	102	47
10	180	50	176	98	42	175	97	47
11	181	50	182	101	42	176	97	47
12	185	50	179	97	41	181	98	47
13	186	50	182	98	41	179	96	47
16	191	50	186	97	41	183	96	47
20	205	50	197	96	41	193	94	45
24	209	50	203	97	41	199	95	44
28	211	50	200	95	39	191	91	43
32	220	50	206	94	39	195	89	43
36	228	50	210	92	39	195	86	43
40	232	50	211	91	39	193	83	43
44	236	50	208	88	39	193	82	43
48	237	50	211	89	39	196	83	41
52	237	50	206	87	39	192	81	40
56	246	50	212	86	39	192	78	40
60	242	50	209	86	39	187	77	40
64	253	50	214	85	39	191	76	40
68	261	49	214	82	38	185	71	39
72	267	49	215	81	38	189	71	37
76	275	48	218	79	36	190	69	35
80	277	47	216	78	36	184	66	30
84	284	45	216	76	35	189	67	28
88	282	45	215	76	34	192	68	26
92	286	44	214	75	30	189	66	23
96	291	41	216	74	30	196	67	20
100	293	41	218	74	26	208	71	15
104	297	38	219	74	23	224	75	10

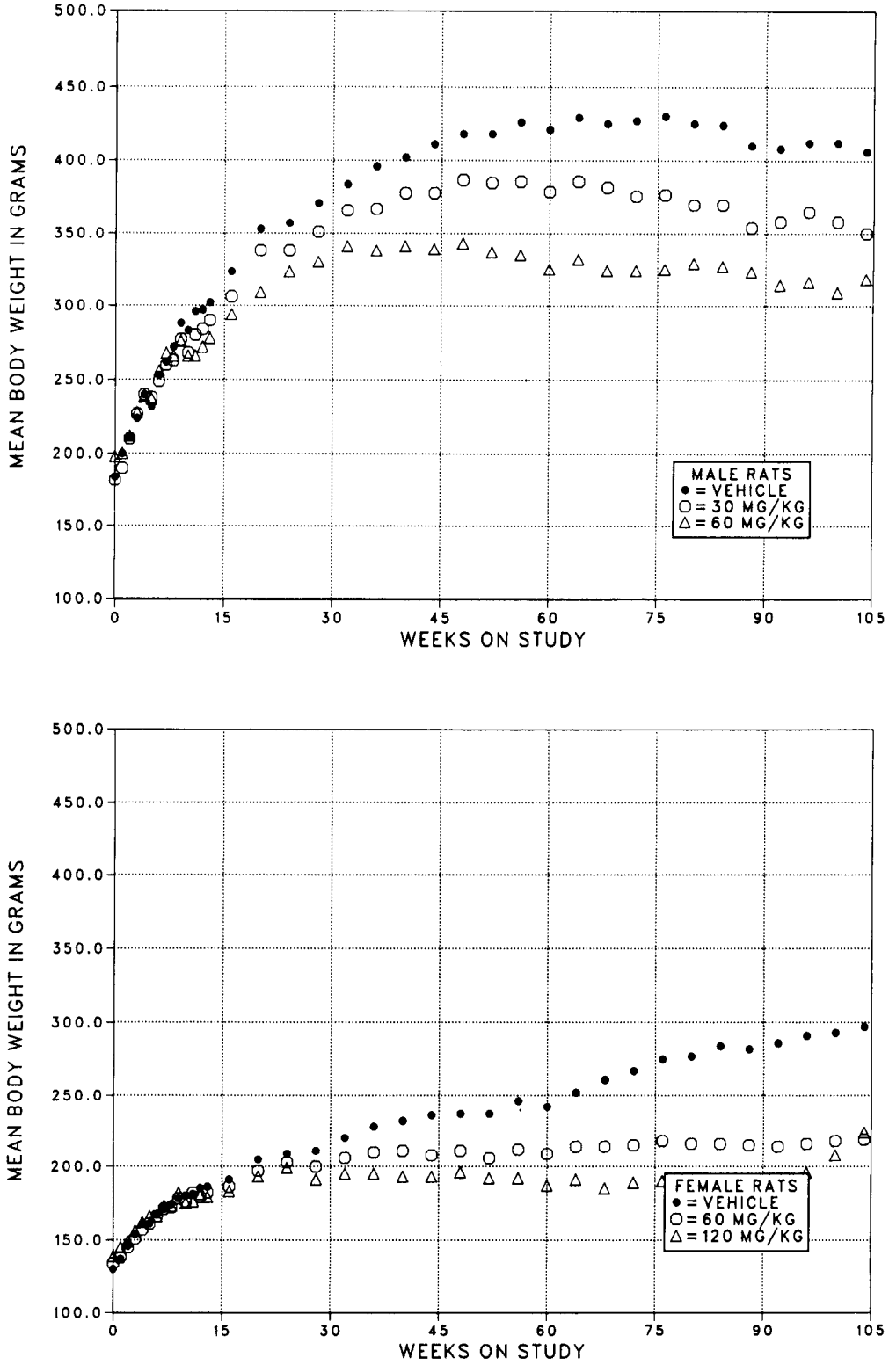


Figure 3. Growth Curves for Rats Administered Toluene Diisocyanate in Corn Oil by Gavage

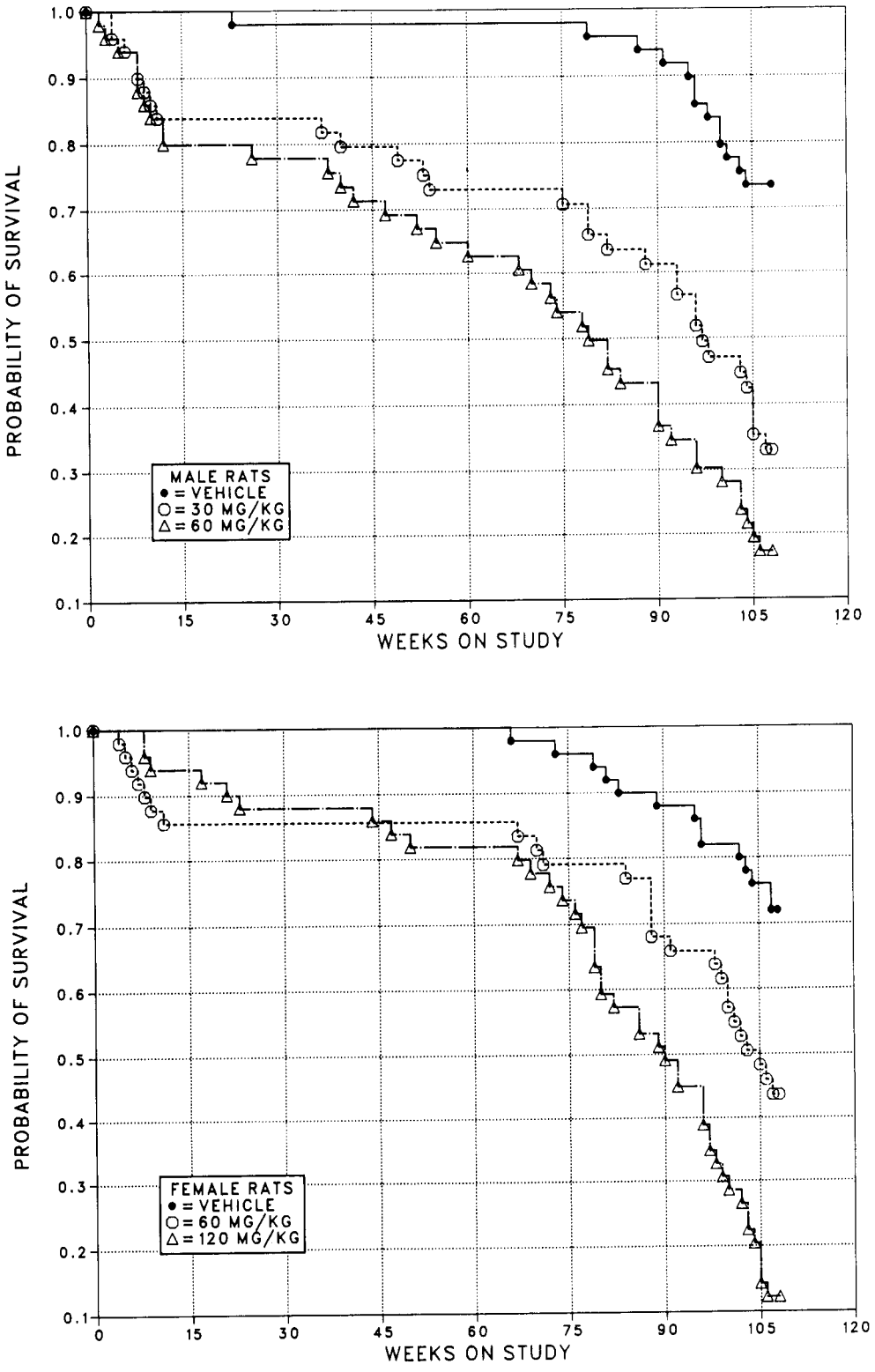


Figure 4. Kaplan-Meier Survival Curves for Rats Administered Toluene Diisocyanate in Corn Oil by Gavage

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Appendix Tables A3 and A4 give the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Historical incidences of tumors in control animals are listed in Appendix E. Because of the reduced survival observed in dosed groups relative to controls, a direct comparison of overall tumor incidences in dosed groups and historical controls may be misleading. The historical control data are included primarily to determine how representative the tumor incidences observed in concurrent vehicle controls are with respect to other studies in the bioassay program. Appendix F, Tables F1 and F2, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix F (footnotes).

Untreated Controls: At week 87 untreated controls were sacrificed and examined. The incidence and type of tumors in individual rats did not appear different from the normal background of tumors in the F344/N rat. Thus these data are not given in this report.

Subcutaneous Tissue: Fibromas or fibrosarcomas occurred in male rats with a statistically significant positive trend, and the incidence in the high dose males was significantly higher than that in the controls (Table 6). (See Appendix E, Table E1 for a comparison of these test incidences with a combined historical control rate of 6.5%.)

Fibromas or fibrosarcomas also occurred in female rats with a statistically significant positive trend, and the incidence in the high dose females was higher than that in the controls by life table analysis (Table 6). (See Appendix E, Table E2 for a comparison of these test incidences with a combined historical control rate of 1.6%.)

Mammary Gland: By life table and incidental tumor test analyses, there were statistically significant increases in the incidence of combined mammary gland tumors in female rats in both low dose and high dose groups (Table 7). Since these mammary gland tumors and subcutaneous tissue tumors were all found in the axillary and inguinal areas, they are regarded as all arising from mammary tissue. The survival-adjusted tumor incidences provide a more meaningful comparison than unadjusted overall tumor rates. For example, the first tumor was seen in an animal dying at week 84, and the proportions of animals surviving at least to week 84 with combined mammary gland tumors were: controls, 17/45 (38%); low dose, 25/36 (69%); and high dose, 21/28 (75%). See Appendix E, Table E3 for a comparison of these test incidences with a historical control rate of 23% for combined mammary gland tumors.

There we no differences in the incidence of mammary gland fibroadenomas in male rats after 30 or 60 mg/kg TDI treatment compared to controls (Appendix F, Table F1).

TABLE 6. INCIDENCES OF RATS WITH SUBCUTANEOUS TUMORS

	MALES		
	Vehicle Control	30 mg/kg	60 mg/kg
Fibroma			
Overall Incidence	3/50 (6%)	3/50 (6%)	9/50 (18%)
Adjusted Incidence	8.3%	16.5%	56.6%
Terminal Incidence	3/36 (8%)	1/14 (7%)	3/8 (38%)
Life Table Test	P<0.001	P=0.258	P<0.001
Incidental Tumor Test	P=0.002	P=0.415	P=0.004
Fibrosarcoma			
Overall Incidence	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Incidence	0.0%	19.0%	23.1%
Terminal Incidence	0/36 (0%)	2/14 (14%)	0/8 (0%)
Life Table Test	P=0.003	P=0.020	P=0.008
Incidental Tumor Test	P=0.021	P=0.044	P=0.089
Fibroma or Fibrosarcoma			
Overall Incidence	3/50 (6%)	6/50 (12%)	12/50 (24%)
Adjusted Incidence	8.3%	33.5%	66.6%
Terminal Incidence	3/36 (8%)	3/14 (21%)	3/8 (38%)
Life Table Test	P<0.001	P=0.016	P<0.001
Incidental Tumor Test	P<0.001	P=0.056	P<0.001

	FEMALES		
	Vehicle Control	60 mg/kg	120 mg/kg
Fibroma			
Overall Incidence	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Incidence	0.0%	5.3%	35.7%
Terminal Incidence	0/36 (0%)	1/19 (5%)	1/6 (17%)
Life Table Test	P<0.001	P=0.373	P=0.001
Incidental Tumor Test	P=0.019	P=0.373	P=0.083
Fibroma or Fibrosarcoma			
Overall Incidence	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted Incidence	5.3%	5.3%	51.8%
Terminal Incidence	1/36 (3%)	1/19 (5%)	2/6 (33%)
Life Table Test	P<0.001	P=0.715N	P<0.001
Incidental Tumor Test	P=0.038	P=0.609N	P=0.092

TABLE 7. COMBINED INCIDENCES OF MAMMARY GLAND TUMORS AND SUBCUTANEOUS TISSUE TUMORS IN FEMALE RATS

	Vehicle Control	60 mg/kg	120 mg/kg
Overall Incidence	17/50 (34%)	25/50 (50%)	21/50 (42%)
Adjusted Incidence	43.1%	88.8%	91.1%
Terminal Incidence	14/36 (39%)	16/19 (84%)	4/6 (67%)
Life Table Test	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P<0.001	P=0.009

III. RESULTS: RATS—TWO-YEAR STUDIES

Hematopoietic System: Monocytic leukemia was observed in male and female rats with a statistically significant decreasing trend (Table 8), and the pairwise comparisons between the control and dosed groups were significant. These decreases were not significant by life table analysis. See Appendix E, Tables E4 and E5 for a comparison of these test incidences with a historical control rate of 9.6% (males) and 13.2% (females) for leukemia.

Pancreas: Acinar cell adenomas were observed in male rats with a statistically significant trend, and the incidence in the high dose group was significantly higher than that in the controls (Table 9). See Appendix E, Table E6 for a comparison of these test incidences with a historical control rate of 0.6%. In high dose female rats one acinar cell adenoma and one acinar cell carcinoma were observed.

The adenomas were sharply demarcated from the surrounding tissue and were characterized by a loss of acinar structure, an increase in the number of basophilic cells, and enlarged and irregular nuclei with increased mitotic activity. (Mitoses often averaged one to three per high-power field.) The lesions were usually small, often less than 1 to 2 millimeters in diameter.

A dose-related increase also was observed in the number of male rats with nodular hyperplasia of the pancreatic acinus (control, 0%; low dose, 4%; high dose, 8%).

Islet cell adenomas occurred in female rats with a statistically significant positive trend (Table 9); the incidences of dosed females with these tumors were significantly higher than those in the controls. An islet cell carcinoma was observed in a low dose female rat. (See Appendix E, Table E7 for a comparison of these test incidences with a historical control rate of 0.8% for adenomas and 0.1% for carcinomas.) The markedly reduced survival in high dose female rats may have been responsible for the lower incidence of islet cell tumors in this group relative to the low dose group. In male rats, pancreatic islet cell adenoma or carcinoma (combined) showed a positive trend and increased incidence in the high dose group by the life table test (Table 9).

TABLE 8. INCIDENCES OF MONOCYTIC LEUKEMIA IN RATS

	MALES		
	Vehicle Control	30 mg/kg	60 mg/kg
Overall Incidence	11/50 (22%)	4/50 (8%)	4/50 (8%)
Adjusted Incidence	25.5%	19.0%	19.2%
Terminal Incidence	5/36 (14%)	0/14 (0%)	0/8 (0%)
Life Table Test	P=0.559N	P=0.423N	P=0.574
Incidental Tumor Test	P=0.027N	P=0.053N	P=0.039N

	FEMALES		
	Vehicle Control	60 mg/kg	120 mg/kg
Overall Incidence	21/50 (42%) *(a)*	7/50 (14%)	4/50 (8%)
Adjusted Incidence	47.4%	26.3%	32.9%
Terminal Incidence	13/36 (36%)	2/19 (11%)	1/6 (17%)
Life Table Test	P=0.168N	P=0.120N	P=0.392N
Incidental Tumor Test	P<0.001N	P=0.006N	P=0.001N

(a) One lymphoma was observed in this group.

TABLE 9. INCIDENCES OF PANCREATIC LESIONS IN RATS

	MALES		
	Vehicle Control	30 mg/kg	60 mg/kg
Acinar Cell			
Nodular Hyperplasia	0/47 (0%)	2/47 (4%)	4/49 (8%)
Adenoma			
Overall Incidence	1/47 (2%)	3/47 (6%)	7/49 (14%)
Adjusted Incidence	2.9%	18.2%	59.2%
Terminal Incidence	1/35 (3%)	2/14 (14%)	4/8 (50%)
Life Table Test	P<0.001	P=0.075	P<0.001
Incidental Tumor Test	P<0.001	P=0.128	P=0.001

	MALES		
	Vehicle Control	30 mg/kg	60 mg/kg
Islet Cell			
Adenoma or Carcinoma			
Overall Incidence	1/47 (2%)	0/47 (0%)	4/49 (8%)
Adjusted Incidence	2.9%	0.0%	24.2%
Terminal Incidence	1/35 (3%)	0/14 (0%)	1/8 (13%)
Life Table Test	P=0.007	P=0.682N	P=0.013
Incidental Tumor Test	P=0.075	P=0.682N	P=0.180

	FEMALES		
	Vehicle Control	60 mg/kg	120 mg/kg
Islet Cell			
Adenoma			
Overall Incidence	0/50 (0%)	6/49 (12%) *(a)*	2/47 (4%)
Adjusted Incidence	0.0%	24.2%	33.3%
Terminal Incidence	0/36 (0%)	3/19 (16%)	2/6 (33%)
Life Table Test	P=0.008	P=0.003	P=0.006
Incidental Tumor Test	P=0.054	P=0.010	P=0.006

(a) One islet cell carcinoma was also observed in this group.

Liver: The incidence of female rats with neoplastic nodules occurred with a statistically significant positive trend; the incidence of high dose females with these nodules was significantly higher than that of the controls (Table 10). (See Appendix E, Table E8 for a comparison of these test incidences with a historical control rate of 1.5% for liver tumors.)

Brain: Gliomas were found in two high dose male rats and a pinealoma was found in a third high dose male. (See Appendix E, Table E9 for a comparison of these test incidences with a historical control rate of 1.0% for all brain tumors.)

Lungs: Acute bronchopneumonia was found in increased incidence in dosed rats (males: control, 2/50, 4%; low dose, 6/50, 12%; high dose, 14/50, 28%; females: control, 1/50, 2%; low dose, 10/50, 20%; high dose, 25/49, 51%; Appendix C).

Lung sections were examined from 11 male and 10 female rats that died during the first 4 months of the studies. All lungs showed marked congestion and variable amounts of pulmonary edema. Edema occurred in the bronchioles and alveoli and in a perivascular location. Slight to

TABLE 10. INCIDENCES OF NEOPLASTIC NODULES OF THE LIVER IN FEMALE RATS

	Vehicle Control	60 mg/kg	120 mg/kg
Overall Incidence	3/50 (6%)	8/50 (16%)	8/48 (17%)
Adjusted Incidence	8.0%	30.6%	60.1%
Terminal Incidence	2/36 (6%)	3/19 (16%)	3/6 (50%)
Life Table Test	P<0.001	P=0.014	P<0.001
Incidental Tumor Test	P=0.035	P=0.068	P=0.022

moderate amounts of perivascular lymphoplasmacytosis were observed in four rats. Necrotizing suppurative pneumonia was detected in two rats, and the lungs of one of these animals contained numerous bacteria. Bacteria were also detected in the lungs of two other rats, and a clump of foreign material (presumably of vegetable origin) was found in the bronchus of another animal. Mucocellular exudate was observed in bronchiolar lumens in a moderate number of rats. The presence of trace to very small quantities of pale yellow, slightly refractile material was detected in terminal portions of the respiratory tree (alveoli and terminal bronchioles) in 13/21 lungs examined. In the bronchioles, the material was associated with a stringy pink substance that was suggestive of fibrin and that appeared as an aggregate of vacuoles and strands. Very pale, refractive material was sometimes observed in the vacuoles. Larger, pale yellow, globular bodies were found in respiratory bronchioles and alveoli. The bodies occasionally appeared "fractured" and were sometimes associated with an inflammatory reaction.

SINGLE-DOSE STUDIES

Mortality was proportional to the dose of TDI administered, but the death rate for males was higher than that for females (Table 11). White, crystalline material was found in the stomach at necropsy; this finding was dose related.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED A SINGLE DOSE OF TOLUENE DIISOCYANATE BY GAVAGE

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weights (grams)		
		Initial	Final	Change
MALES				
2,150	5/5	28	30	+2
3,160	5/5	26	25	-1
4,640	1/5 (2,7,7,8)	21	22	+1
6,810	0/5 (2,2,2,4,4)	24	—	—
10,000	0/5 (1,1,1,2,2)	26	—	—
FEMALES				
3,160	5/5	20	20	0
4,640	4/5 (5)	19	18	-1
6,810	1/5 (1,2,2,2)	17	23	+6
10,000	0/5 (1,2,2,2,2)	19	—	—

(a) Number surviving/number per group

FOURTEEN-DAY STUDIES

Two 14-day studies were conducted because all animals in the first study (administered 500 to 4,000 mg/kg) died by day 12.

Doses of 30 to 500 mg/kg were administered to animals in the second study. Deaths and changes in mean body weight gains were not dose related (Table 12).

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED TOLUENE DIISOCYANATE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
MALES					
0	5/5	22	23	+1	—
30	3/5 (8,9)	22	23	+1	0
60	4/5 (8)	22	23	+1	0
120	4/5 (14)	22	24	+2	+ 4
240	4/5 (8)	23	23	0	0
500	3/5 (6,10)	23	24	+1	+ 4
FEMALES					
0	5/5	19	20	+1	—
30	5/5	19	19	0	- 5
60	5/5	19	19	0	- 5
120	5/5	19	20	+1	0
240	3/5 (7,10)	19	22	+3	+10
500	5/5	19	19	0	- 5

(a) Number surviving/number per group

(b) Weight of the dosed group relative to that of the controls = $\frac{\text{Weight (Dosed Group)} - \text{Weight (Control Group)}}{\text{Weight (Control Group)}} \times 100$

THIRTEEN-WEEK STUDIES

Two 13-week studies were conducted, the first using doses of 6 to 100 mg/kg and the second employing doses of 15 to 240 mg/kg. In the first study, decrements in mean body weight gain and food consumption and respiratory noises were interpreted as being related to administration of TDI (Table 13). The second study failed to confirm any of the previous data; only two females administered 240 mg/kg and one female receiving 120 mg/kg died as a result of chemical administration. Livers from two of these animals had necrosis or inflammation, but no compound-related lesions were observed in other mice. The doses for females in the 2-year study (60 and 120 mg/kg) were selected because of the deaths observed in the 13-week studies. Doses of 120 and 240 mg/kg were selected for male mice.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED TOLUENE DIISOCYANATE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)* (Day of Death)	Mean Body Weights (grams)			Final Body Weights Relative to Controls *(b)* (Percent)
		Initial	Final	Change	
		FIRST STUDY			
MALES					
0	6/10 (1,1,1,1)	18	31	+13	—
6	9/10 (1)	17	30	+13	- 3
12	8/10 (1,4)	16	27	+11	-13
25	9/10 (3)	17	25	+ 8	-19
50	9/10 (6)	17	25	+ 8	-19
100	7/10 (1,3,5)	17	23	+ 6	-26
FEMALES					
0	10/10	14	22	+ 8	—
6	9/10 (1)	13	21	+ 8	- 5
12	9/10 (5)	13	20	+ 7	- 9
25	8/10 (1,2)	14	20	+ 6	- 9
50	7/10 (3,4,5)	14	18	+ 4	-18
100	5/10 (1,2,2,2,2)	14	19	+ 5	-14
		SECOND STUDY			
MALES					
0	5/10 *(c)*	18.9	23.6	+ 4.7	—
15	5/10 *(c)*	18.9	27.0	+ 8.1	+14
30	10/10	17.6	26.3	+ 8.7	+11
60	10/10	18.8	26.0	+ 7.2	+10
120	10/10	18.3	26.5	+ 8.2	+12
240	5/10 *(c)*	17.9	25.2	+ 7.3	+ 7
FEMALES					
0	10/10	15.8	21.0	+ 5.2	—
15	10/10	17.1	20.8	+ 3.7	- 1
30	5/10 *(c)*	17.0	20.0	+ 3.0	- 5
60	5/10 *(c)*	16.4	22.2	+ 5.8	+ 6
120	9/10 *(d)*	16.4	21.6	+ 5.2	+ 3
240	8/10 *(e)*	16.0	21.1	+ 5.1	0

(a) Number surviving/number per group

(b) Weight of the dosed group relative to that of the controls =

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

(c) Deaths were due to drowning during week 13

(d) Death was during week 10

(e) Deaths were during weeks 6 and 9

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male mice (throughout the study) and of high dose female mice (after week 56) were lower than those of the controls. The depressions in mean body weight were dose related (Table 14 and Figure 5). No other compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival of male and female mice administered TDI in corn oil at the doses used in these studies, and those of the controls, are shown by the Kaplan and Meier curves in Figure 6. In male mice, the survival of the high dose group was significantly shorter than that of the controls ($P<0.001$) and of the low dose group ($P=0.003$). In female mice, the survival of the high dose group was significantly shorter than that of the low dose group ($P=0.028$). One female control mouse was accidentally killed.

In male mice, 46/50 (92%) of the controls, 40/50 (80%) of the low dose, and 26/50 (52%) of the high dose group lived to the termination period of the study at 107 weeks. In female mice, 34/50 (68%) of the controls, 43/50 (86%) of the low dose, and 33/50 (66%) of the high dose group lived to the termination period of the study at 107 weeks.

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Appendix Tables B3 and B4 give the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Historical incidences of tumors in control animals are listed in Appendix E. Because of the reduced survival observed in dosed groups relative to controls, a direct comparison of overall tumor incidences in dosed groups and historical controls may be misleading. The historical control data are included primarily to determine how representative the tumor incidences observed in concurrent vehicle controls are with respect to other studies in the bioassay program. Appendix F, Tables F3 and F4, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in chapter II (Data Recording and Statistical Methods) and Appendix F (footnotes).

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF TOLUENE DIISOCYANATE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of veh controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of veh controls)	High Dose No. of Survivors
MALE								
0	24.5	50	24.9	102	50	25.1	102	50
1	26.3	50	25.6	97	50	24.7	94	49
2	27.0	50	27.1	100	50	25.4	94	49
3	26.9	50	26.6	99	50	26.2	97	49
4	29.0	50	--	--	--	25.2	87	46
5	29.4	50	27.1	92	50	26.4	90	44
6	29.8	50	28.6	96	47	26.4	89	44
7	30.0	50	29.0	97	47	27.3	91	44
8	31.1	50	30.1	97	47	28.3	91	44
9	31.7	50	30.8	97	47	29.3	92	44
10	30.9	50	30.3	98	47	29.0	94	44
11	32.0	50	31.1	97	47	29.4	92	44
12	32.3	50	31.0	96	47	28.8	89	44
13	31.9	50	30.1	94	47	28.9	91	44
16	32.8	50	31.0	95	47	29.6	90	43
20	33.6	50	32.8	98	46	30.0	89	43
24	34.3	50	33.0	96	46	30.0	87	42
28	36.0	50	33.7	94	46	31.4	87	41
32	34.5	50	33.6	97	46	32.6	94	41
36	36.5	50	35.9	98	46	34.6	90	41
40	36.0	50	36.0	95	46	34.1	90	41
44	36.9	50	36.7	94	46	34.2	88	41
48	37.7	50	35.8	95	46	33.8	90	41
52	37.5	50	35.7	95	46	33.2	89	40
56	37.4	50	35.9	96	46	33.4	89	40
60	36.0	50	36.3	96	46	33.6	88	40
64	37.5	50	36.1	96	46	32.9	88	40
68	36.0	50	36.3	96	46	33.4	88	40
72	38.8	50	37.2	96	46	34.8	90	40
76	37.8	50	37.0	98	45	34.4	91	39
80	39.7	50	37.0	93	45	33.2	84	36
84	39.6	50	37.5	94	45	34.4	86	34
88	38.9	49	36.7	94	45	33.9	87	33
92	38.6	49	36.2	93	45	33.6	87	33
96	38.4	47	36.2	94	42	33.9	88	31
100	36.9	47	35.4	96	40	33.0	89	30
104	36.1	46	35.1	97	40	32.8	91	29
FEMALE								
0	19.3	50	19.2	99	50	19.5	101	50
1	20.5	50	18.3	89	50	18.1	88	49
2	21.0	50	20.0	95	48	19.8	94	45
3	21.5	50	21.0	98	48	20.3	94	44
4	22.2	50	21.7	98	48	20.3	91	41
5	22.0	50	21.7	99	48	21.7	99	41
6	22.2	50	21.8	98	48	21.6	97	41
7	22.1	50	22.6	102	48	22.3	101	41
8	23.1	50	23.1	100	48	23.5	102	40
9	24.4	50	23.6	97	48	23.9	98	40
10	23.8	50	23.5	99	48	24.2	102	40
11	23.8	50	23.9	100	48	24.2	102	40
12	23.8	50	23.5	99	48	23.8	100	40
13	23.4	50	23.3	100	48	24.1	103	40
16	23.6	50	23.9	101	48	24.5	104	40
20	24.7	50	24.7	100	47	24.6	100	40
24	25.0	50	25.0	100	47	25.0	100	40
28	26.0	50	26.5	102	47	26.7	103	40
32	27.5	50	27.7	101	47	27.4	100	40
36	29.0	50	29.1	100	47	28.6	99	40
40	29.4	50	30.1	102	47	29.5	100	40
44-45	30.0	50	30.2	101	47	28.9	96	40
48	29.3	50	29.7	101	47	28.5	97	40
52	29.4	50	29.8	101	47	28.7	98	40
56	29.5	50	30.4	103	47	29.1	99	40
60	30.7	50	30.8	100	47	29.0	94	40
64	31.4	50	31.4	100	47	30.0	96	40
68	31.7	50	31.8	100	47	30.2	95	39
72	32.8	49	33.3	102	47	31.6	96	39
76	33.0	47	33.5	102	47	31.7	96	39
80	34.9	45	34.5	99	45	31.8	91	39
84	34.4	45	35.2	102	45	31.9	93	38
88	34.8	44	34.6	99	45	31.4	90	38
92	34.8	42	34.8	100	45	31.1	89	37
96	34.9	40	34.4	99	45	31.6	91	37
100	34.2	39	33.4	98	45	31.2	91	34
104	33.9	34	32.7	96	44	31.0	91	33

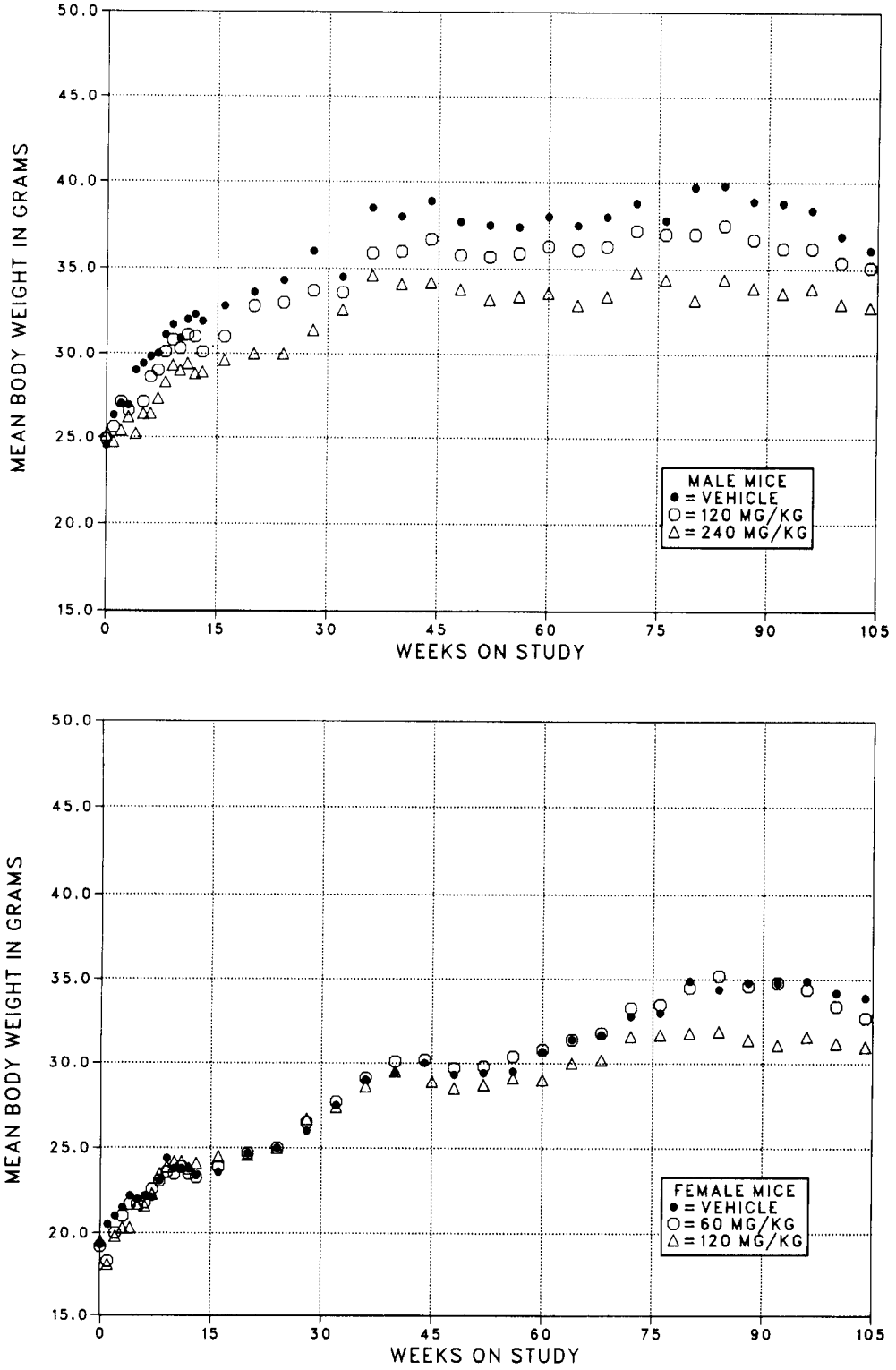


Figure 5. Growth Curves for Mice Administered Toluene Diisocyanate in Corn Oil by Gavage

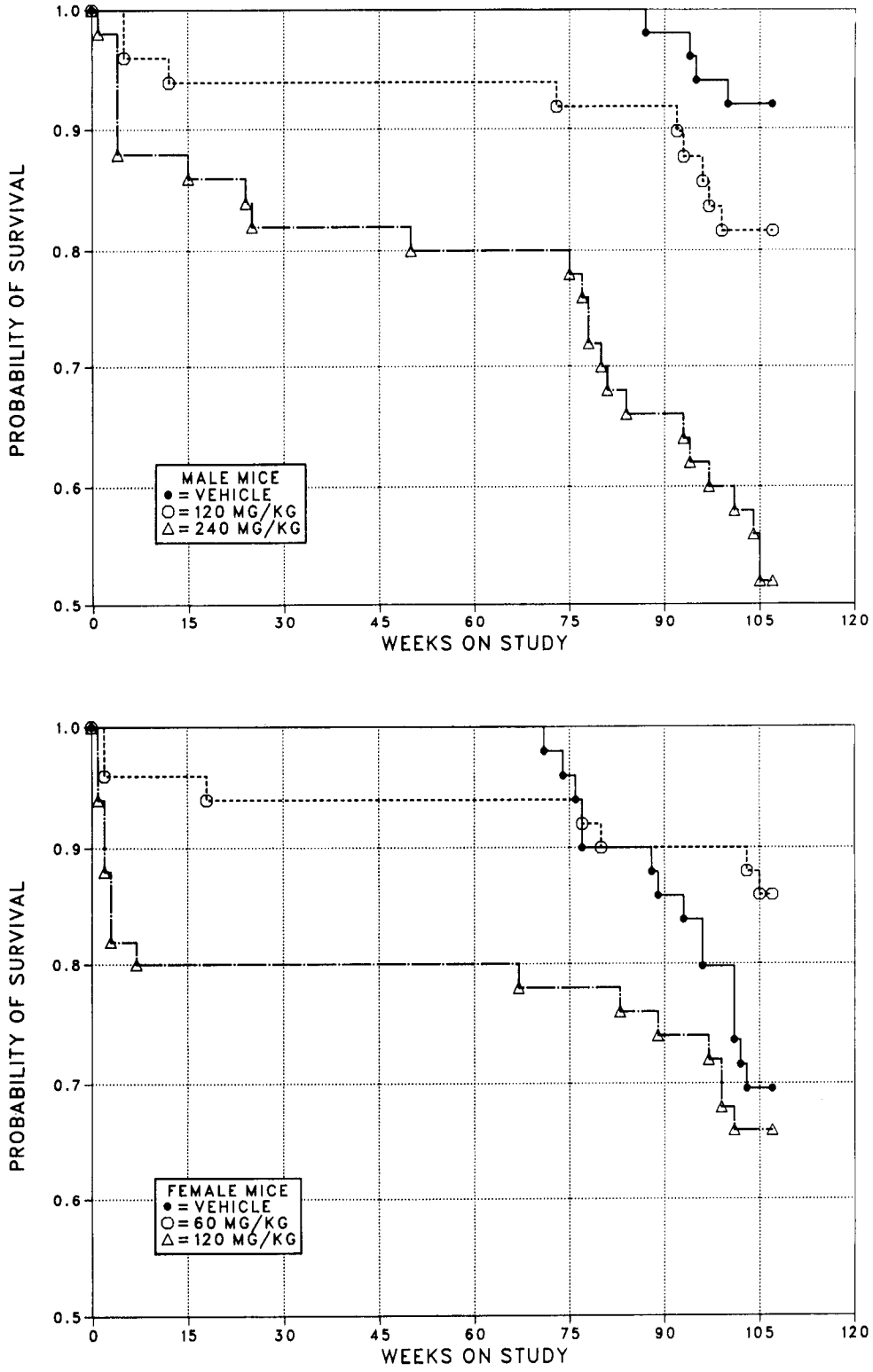


Figure 6. Kaplan-Meier Survival Curves for Mice Administered Toluene Diisocyanate in Corn Oil by Gavage

Untreated Controls: At week 87 untreated controls were sacrificed and examined. The incidence and type of tumors in individual mice did not appear different from the normal background of tumors in the $B6C3F_1$ mouse. Thus these data are not given in this report.

In male mice, no tumors occurred at statistically significant incidences.

Circulatory System: Hemangiosarcomas (of the liver, ovaries, or peritoneum) were observed with a statistically significant positive trend in female mice (Table 15). The combined incidences of hemangiomas (of the spleen, or subcutaneous tissue) or hemangiosarcomas occurred with a statistically significant positive trend, and the results of pairwise comparisons between the control and high dose groups were significant. (See Appendix E, Table E10 for a comparison of these test incidences with a combined historical control rate of 2.9%.)

TABLE 15. INCIDENCES OF FEMALE MICE WITH TUMORS OF THE CIRCULATORY SYSTEM

	Vehicle Control	60 mg/kg	120 mg/kg
Hemangiosarcoma			
Overall Incidence	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Incidence	0.0%	0.0%	8.0%
Terminal Incidence	0/34 (0%)	0/43 (0%)	0/33 (0%)
Life Table Test	P=0.029	—	P=0.105
Incidental Tumor Test	P=0.015	—	P=0.037
Hemangioma or Hemangiosarcoma			
Overall Incidence	0/50 (0%)	1/50 (2%)	5/50 (10%)
Adjusted Incidence	0.0%	2.3%	13.3%
Terminal Incidence	0/34 (0%)	1/43 (2%)	1/33 (3%)
Life Table Test	P=0.008	P=0.547	P=0.029
Incidental Tumor Test	P=0.003	P=0.547	P=0.005

Liver: Hepatocellular adenomas occurred in female mice with a statistically significant positive trend, and the pairwise comparisons between the control and high dose groups were significant (Table 16). Adenomas or carcinomas (combined) occurred with a significant positive trend, and the results of pairwise comparisons between the control and high dose groups were significant. See Appendix E, Table E11 for a comparison of these test incidences with a combined historical control rate of 6.7%.

Hematopoietic System: Leukemia was observed in female mice with a statistically significant, decreasing trend (Table 17). The results of pairwise comparisons were not significant. Malignant lymphoma in female mice was observed with a statistically significant, increasing trend, and the results of pairwise comparisons between the control and high dose group were significant. The incidence of leukemia or lymphoma (combined) was not significantly different for dosed or control male or female mice.

Kidney: Cytomegaly, mainly in tubules near the corticomedullary junction, was observed in 45/48 (94%) low dose male mice and 41/50 (82%) high dose male mice compared with 0/50 in the controls.

TABLE 16. INCIDENCES OF FEMALE MICE WITH LIVER TUMORS

	Vehicle Control	60 mg/kg	120 mg/kg
Hepatocellular Adenoma			
Overall Incidence	2/50 (4%)	3/50 (6%)	12/50 (24%)
Adjusted Incidence	5.3%	6.7%	36.4%
Terminal Incidence	1/34 (3%)	2/43 (5%)	12/33 (36%)
Life Table Test	P<0.001	P=0.571	P=0.003
Incidental Tumor Test	P<0.001	P=0.325	P=0.003
Hepatocellular Carcinoma			
Overall Incidence	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Incidence	5.0%	4.7%	8.8%
Terminal Incidence	1/34 (3%)	2/43 (5%)	2/33 (6%)
Life Table Test	P=0.376	P=0.629N	P=0.463
Incidental Tumor Test	P=0.248	P=0.644	P=0.308
Hepatocellular Adenoma or Carcinoma			
Overall Incidence	4/50 (8%)	5/50 (10%)	15/50 (30%)
Adjusted Incidence	10.1%	11.2%	44.1%
Terminal Incidence	2/34 (6%)	4/43 (9%)	14/33 (42%)
Life Table Test	P=0.001	P=0.601	P=0.004
Incidental Tumor Test	P<0.001	P=0.321	P=0.001

TABLE 17. INCIDENCES OF FEMALE MICE WITH TUMORS OF THE HEMATOPOIETIC SYSTEM

	Vehicle Control	60 mg/kg	120 mg/kg
Leukemia			
Overall Incidence	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Incidence	7.4%	0.0%	0.0%
Terminal Incidence	0/34 (0%)	0/43 (0%)	0/33 (0%)
Life Table Test	P=0.040N	P=0.102N	P=0.147N
Incidental Tumor Test	P=0.119N	P=0.414N	P=0.240N
Malignant Lymphoma			
Overall Incidence	10/50 (20%)	17/50 (34%)	16/50 (32%)
Adjusted Incidence	25.8%	38.6%	44.2%
Terminal Incidence	7/34 (21%)	16/43 (37%)	13/33 (39%)
Life Table Test	P=0.082	P=0.241	P=0.101
Incidental Tumor Test	P=0.029	P=0.085	P=0.033
Lymphoma or Leukemia			
Overall Incidence	13/50 (26%)	17/50 (34%)	16/50 (32%)
Adjusted Incidence	31.3%	38.6%	44.2%
Terminal Incidence	7/34 (21%)	16/43 (37%)	13/33 (39%)
Life Table Test	P=0.241	P=0.503	P=0.273
Incidental Tumor Test	P=0.089	P=0.151	P=0.098

IV. DISCUSSION AND CONCLUSIONS

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Because the 2,4 (80%)/2,6 (20%)-toluene diisocyanate (TDI) reacted with the moisture in the corn oil vehicle, the doses received by rats and mice in the 2-year studies were reduced to 77% to 90% of the target doses (female rats and mice: 60 or 120 mg/kg; male rats: 30 or 60 mg/kg; male mice: 120 or 240 mg/kg). Despite the reduced doses, mean body weight gains of male and female rats were less than those of the controls after week 20. Early deaths occurred in groups of dosed male and female rats, but by week 60 only the high dose male rats were dying as a result of TDI administration. At this time, a decision was made to continue the studies of rats; however, an apparent dose-related pattern of mortality began to emerge at week 70, and persisted until the end of the study. The delayed cumulative toxicity caused by TDI administration indicated that the estimated maximum tolerated doses had been exceeded in rats. Mortality in male mice was also dose related and significantly higher than in controls, but it was not as excessive as that in rats.

Bronchopneumonia was the most prominent nonneoplastic effect seen in the short-term and 2-year phases of these gavage studies. The respiratory effects observed were similar to those seen in rats exposed by inhalation to TDI at a concentration of 0.1 ppm for 6 hours per day, once per week, for 38 weeks: tracheitis, bronchitis, pneumonia, and purulent bronchiectasis (Niewenhuis et al., 1965). The major lesion was described as a fibrous tissue proliferation, often blocking the bronchioles, and was similar to what has been described in animals exposed to higher concentrations of inhaled TDI (Duncan et al., 1962). The control rats in the Niewenhuis study also had mild to marked pneumonitis. Loeser (1983) observed dose-related respiratory tract irritation in mice exposed by vapor inhalation to 2,4-/2,6-TDI (80/20) at 0.05 or 0.15 ppm for 2 years; none was apparently found in rats.

TDI stimulates the trigeminal nerve and is one of the more potent sensory irritants (Sangha and Alarie, 1979). Occupational asthma, or reversible obstruction of the airways in response to TDI, has been seen in workers exposed to the chemical (Weil et al., 1981). Workers exposed to TDI at concentrations of less than 0.1 ppm had marked declines in forced respiratory volume, with reductions in the ratio of forced expiratory volume to forced vital capacity; forced expiratory flow was 25%-50% of the forced vital capacity. Bronchial hypersensitivity to TDI developed in 4.3% of these workers, but there were no predictive indices for this response. Respiratory hypersensitivity has been shown to develop in guinea pigs exposed to 0.005 ppm TDI after dermal contact with the chemical (Karol et al., 1981).

In the present study, the late-appearing pattern of mortality in rats could be a reflection of delayed hypersensitivity, as well as direct respiratory irritation. The incidences of bronchopneumonia were dose related in male and female rats, and this effect may have weakened the animals' resistance to further chemical challenge. The increased rate of mortality may also be due, in part, to TDI's inhibition of acetylcholinesterase, which could have compounded the animals' respiratory difficulty (Brown et al., 1982). The study by Brown and co-workers showed that 2,6-toluene diisocyanate was 60 times more effective than the 2,4-isomer in inhibiting human serum cholinesterase. The commercial mixture of TDI used in the present studies consisted of 80% 2,4-isomer and 20% 2,6-isomer, the latter being the active enzyme inhibitor.

Despite the reduced survival, there was unequivocal evidence of dose-related increases in tumors in rats and mice in the 2-year studies. About 50% of the tumors detected were observed in animals killed at the end of these studies; the rest were found in animals dying between weeks 77 and 108.

Tissues associated with the digestive system were primary sites of tumor induction and included acinar cell adenomas of the pancreas in male rats, and liver tumors in female rats and mice. There were also increased incidences of islet cell adenomas in low dose female rats. Dose-related increases were observed in the number of male rats with nodular hyperplasia of the pancreatic acinus (control, 0%; low dose, 4%; high dose, 8%) and in the incidence of acinar cell adenomas (control, 2%; low dose, 6%; high dose, 14%). The corn oil vehicle used in these gavage studies may have contributed to the incidences of acinar cell tumors in male and female rats. High dietary fat levels were shown to enhance the carcinogenic effect of azaserine in rat pancreas (Longnecker et al., 1981; Roebuck et al. 1981), and enhanced pancreatic tumorigenesis occurred in rats pretreated with azaserine whose diets were supplemented with 20% corn oil (Longnecker et al., 1979). The National Toxicology Program reexamined pancreata of untreated and corn oil gavage control male rats from 37 chronic studies and found a positive association between corn oil administration and the increased incidence of acinar cell hyperplasia, adenoma, and carcinoma of the pancreas

(Boorman and Eustis, 1984). However, further evaluation of the data revealed the increased incidences of pancreatic cell adenoma in the corn oil gavage control male rats were also associated with elevated body weights relative to untreated controls (Haseman et al., 1985). There was no such relationship here since depression of body weight gain commenced at 10-20 weeks TDI treatment, and was dose-related throughout the remainder of the study.

The systemic nature of the carcinogenicity of TDI was demonstrated by the appearance of tumors at multiple sites in male rats (fibromas and fibrosarcomas of the skin), in female rats (mammary gland fibroadenomas, adenomas, papillary adenomas, cystadenomas and subcutaneous fibroadenomas and fibromas), and in female mice (hemangiomas and hemangiosarcomas).

The tumors observed in the liver, pancreas, mammary gland, and subcutaneous tissues of F344/N rats in these studies are the same type as those seen when 2,4-diaminotoluene—a possible hydrolysis product of 2,4-toluene diisocyanate—was administered to the same strain (NCI, 1979). In the 2,4-diaminotoluene study, increased incidences of neoplastic nodules and hepatocellular carcinomas were found in males fed diets containing 79 or 176 ppm and in females fed 171 ppm. Increased incidences of pancreatic acinar cell adenomas were observed in dosed males and in females that received 171 ppm. The incidences of mammary gland fibroadenomas in females were 10-fold greater in the low and high dose groups compared with controls. Furthermore, subcutaneous fibromas were found at significantly increased incidences relative to controls in dosed male rats.

In addition, 2,4-diaminotoluene causes increases in hemangiomas and hemangiosarcomas in male mice and significant increases in hepatocellular neoplasms in both sexes of mice. Although TDI caused the same type of neoplasms in the present study, they were seen in female mice but not in males. There are no available metabolic data that might account for this difference in response. A probable hydrolysis product of 2,6-toluene diisocyanate (2,6-diaminotoluene) was not considered to be carcinogenic for F344/N rats or $B6C3F_1$ mice (NTP, 1980).

Disposition studies of 2,6-TDI in F344 rats showed that the majority of a ^{14}C labelled 60 mg/kg dose administered by gavage was excreted in urine and feces, accounting for 67%-78% of the dosage in 72 hours (RTI, 1985). Very low amounts of ^{14}C were recovered in tissues, ranging from 0.012% to 0.16% of the dose recovered in blood, muscle, skin, adipose tissue, liver, and kidney. At 24 hours after treatment, about 10% of the administered dosage was recovered in urine. The major urinary metabolite was identified by HPLC and confirmed by mass spectrometry and reverse isotopic dilution techniques. More than half (54%) of the 2,6-TDI-derived material in urinary ^{14}C was 2,6-bis (acetylamino)toluene, suggesting the parent 2,6-TDI was hydrolyzed to 2,6-diaminotoluene which was subsequently acetylated and excreted.

Other noteworthy effects observed in rats in the current studies included the brain tumors found in high dose males (two had gliomas and one had a pinealoma). Gliomas have been found in 3/995 controls in the bioassay program and pinealomas have not been previously diagnosed (Appendix E, Table E9). The evidence suggests a possible association between these tumors and administration of TDI.

Differences in mean body weight gains, hypersensitivity, and the incidences of neoplastic and nonneoplastic lesions in animals in the present studies emphasize differences in the degree to which TDI is toxic in different species and sexes. Both female rats and female mice received doses of 60 or 120 mg/kg, and most of the rats died during the study. Male mice received higher doses (120 and 240 mg/kg) than male rats (30 and 60 mg/kg), yet mortality and decreases in mean body weights were less severe in the former group, and no tumors were detected at statistically significant incidences in male mice. Male and female rats and female mice showed positive evidence of carcinogenicity associated with TDI administration. The species and sex differences in sensitivity to TDI may be metabolic, but no experimental data are available.

Loeser (1983) exposed groups of 126 male and female Sprague-Dawley CD rats and 120 CD-1 mice of each sex to 0, 0.05, or 0.15 ppm 2,4-/2,6-toluene diisocyanate (80/20) for 6 hr/day, 5 days/wk by whole-body vapor inhalation for 108-110 weeks (rats) or 104 weeks (mice). Survival for rats was similar among groups at the end of the study (males: controls, 35%; low-dose, 33%; high dose, 29%; females: 32%, 25%, 36%). Survival for mice at study termination was: male mice—controls, 22%; low dose, 30%; high dose, 30%; female mice—40%, 23%, 26%. In both sexes of rats there was a dose-related increase in the incidence of rhinitis in the anterior portion of

the nasal cavity. The lesions were characterized by squamous metaplasia and hyperplasia of the epithelium, variably accompanied by leukocytic infiltration in the lamina propria and exudate in the lumen. For mice, chronic or necrotic rhinitis was common in exposed groups, with lesser lesions of the lower respiratory tract (bronchitis) and eyes, particularly in the 0.15 ppm group. No evidence of TDI-associated benign or malignant tumor induction was reported. The exposure levels used by Loeser correspond to daily gavage doses of less than 1 mg/kg, even assuming 100% retention of inhaled TDI, and may not have been optimal doses to adequately detect a potential carcinogenic response.

There are also conflicting reports about the mutagenicity of TDI. Anderson and Styles (1978) originally reported that 2,4-toluene diisocyanate of unknown purity was non-mutagenic in a study of 120 chemicals performed by Purchase et al. (1978), but several known mutagens were also reported as negative, suggesting a lack of definition in these studies. Andersen et al. (1980) later optimized the procedure for testing volatile isocyanates, and in a study with adequate positive and negative controls showed that a mixture of 2,4- and 2,6-toluene diisocyanate (Desmodur T80) caused a dose-dependent mutagenic response utilizing S-9 activation in *Salmonella typhimurium* strains TA98, TA100, and TA1538. The positive control was 2,4-diaminotoluene, a probable hydrolysis product of 2,4-toluene diisocyanate, which Ames et al. (1975) reported to be mutagenic. In the NTP tests, both 2,6-TDI and a mixture of 2,4- and 2,6-TDI were mutagenic in *Salmonella typhimurium* strains TA98 and TA100 in the presence (but not the absence) of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9. Neither sample was mutagenic in *S. typhimurium* strains TA1535 or TA1537 with or without metabolic activation (Appendix L). Loeser (1983) reported the results of a micronucleus test as showing no dose- or treatment-related percentage increase of micronucleated erythrocytes from rats and mice exposed to 0.05 or 0.15 ppm (v/v) TDI vapor for four weeks (6 hr/day, 5 days/wk).

Toxicology studies with 4,4'-diphenylmethane diisocyanate (MDI) were recently deferred by NTP because of problems similar to those encountered with TDI—difficulties with dose preparation and unexplained toxicity in the short-term studies. For an adequate examination of the toxic reponses to this class of chemicals, particularly to define the metabolism and to evaluate the biochemical and immunological toxicity, it would be necessary to conduct further tests at lower dose levels. Such a comparison of the toxicological properties of TDI, MDI, and other commercially important isocyanates in polyurethane production would be useful, since annual production of these exceeds 1 million tons (Sangha and Alarie, 1979) and only limited toxicological information is available (Woolrich, 1982). It would be preferable to test these chemicals by the inhalation route, since potential human exposure occurs primarily during their production (Weil et al., 1981) or during fires, when the pyrolysis products of polyurethanes are released. Woolley and Raftery (1976) stated that the yellow smoke released during decomposition of flexible polyurethane foam at 200°-300°C appeared to be a polymerized form of TDI. In another study, results of gas chromatographic analysis and mass spectrometry indicated that toluene monoisocyanate was the major decomposition product from combustion of flexible polyurethane foams (Alarie et al., 1975). A report on the occupational hazards of firefighting specifically cites the dangers of exposure to isocyanates produced from the combustion of polyurethane or encountered as neat chemical (Axford et al., 1976).

In summary, the commercial mixture of 2,4- and 2,6-toluene diisocyanate has been shown to produce a variety of toxic effects in humans and animals, including asthma, decreased respiratory function, delayed pulmonary hypersensitivity, bronchopneumonia, and inhibition of acetylcholinesterase. A possible hydrolysis product (2,4-diaminotoluene) of the 2,4-isomer and the mixture of the 2,4- and the 2,6-isomers of TDI have been shown to be mutagenic. In the present studies, the pattern of multifocal tumors was similar to the carcinogenic responses produced by the hydrolysis product of the 2,4-isomer.

Conclusions: Under the conditions of these gavage studies, commercial grade toluene diisocyanate in corn oil was carcinogenic for F344/N rats, causing subcutaneous fibromas and fibrosarcomas (combined) in males and females, pancreatic acinar cell adenomas in males, and pancreatic islet cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in females. Toluene diisocyanate was not carcinogenic for male mice. TDI was carcinogenic for female B6C3F$_1$ mice, causing hemangiomas or hemangiosarcomas (combined) as well as hepatocellular adenomas.

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APPENDIX A

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

TABLE A1.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS			1 (2%)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
SQUAMOUS CELL CARCINOMA			1 (2%)
TRICHOEPITHELIOMA	1 (2%)		
KERATOACANTHOMA	1 (2%)		1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL TUMOR	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)		
SARCOMA, NOS	1 (2%)		
FIBROMA	3 (6%)	3 (6%)	9 (18%)
FIBROSARCOMA		3 (6%)	3 (6%)
FIBROSARCOMA, INVASIVE		1 (2%)	
FIBROADENOMA		1 (2%)	
MESOTHELIOMA, INVASIVE			1 (2%)
OSTEOSARCOMA		1 (2%)	
NEURILEMOMA, MALIGNANT			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MONOCYTIC LEUKEMIA	11 (22%)	4 (8%)	4 (8%)
*MEDIASTINUM	(50)	(50)	(50)
THYMOMA	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(27)	(37)	(36)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (4%)		
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMANGIOSARCOMA, INVASIVE		1 (2%)	
#HEART	(50)	(50)	(50)
NEUROFIBROMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#SUBMAXILLARY GLAND	(50)	(50)	(48)
SARCOMA, NOS		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	7 (14%)	2 (4%)	2 (4%)
HEPATOCELLULAR CARCINOMA		1 (2%)	2 (4%)
#PANCREAS	(47)	(47)	(49)
ACINAR-CELL ADENOMA	1 (2%)	3 (6%)	7 (14%)
#STOMACH	(49)	(49)	(47)
MESOTHELIOMA, METASTATIC	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
PHEOCHROMOCYTOMA, METASTATIC			1 (2%)
FIBROSARCOMA, METASTATIC		1 (2%)	
NEPHROBLASTOMA			1 (2%)
#PERIRENAL TISSUE	(50)	(48)	(49)
LIPOMA	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(44)	(49)
ADENOMA, NOS	2 (4%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CHROMOPHOBE ADENOMA	3 (6%)	4 (9%)	7 (14%)
CHROMOPHOBE CARCINOMA	1 (2%)		1 (2%)
#ADRENAL	(50)	(49)	(50)
CORTICAL CARCINOMA	1 (2%)		
PHEOCHROMOCYTOMA	12 (24%)	7 (14%)	6 (12%)
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
GANGLIONEUROMA	1 (2%)		
#THYROID	(46)	(49)	(47)
C-CELL ADENOMA	2 (4%)	2 (4%)	
C-CELL CARCINOMA	1 (2%)	2 (4%)	2 (4%)
#PARATHYROID	(34)	(36)	(33)
ADENOMA, NOS			1 (3%)
#PANCREATIC ISLETS	(47)	(47)	(49)
ISLET-CELL ADENOMA	1 (2%)		2 (4%)
ISLET-CELL CARCINOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	7 (14%)	1 (2%)	3 (6%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	7 (14%)		1 (2%)
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	48 (96%)	35 (70%)	29 (58%)
INTERSTITIAL-CELL TUMOR, MALIGNA			1 (2%)
MESOTHELIOMA, NOS		2 (4%)	
MESOTHELIOMA, MALIGNANT	2 (4%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
CHROMOPHOBE CARCINOMA, INVASIVE			1 (2%)
PINEALOMA			1 (2%)
GLIOMA, NOS			2 (4%)
SPECIAL SENSE ORGANS			
*EAR	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*ABDOMINAL MUSCLE	(50)	(50)	(50)
FIBROSARCOMA	1 (2%)		
*CARTILAGE,NOS	(50)	(50)	(50)
LIPOMA	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV	1 (2%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR, METASTA			1 (2%)
*PERITONEAL CAVITY	(50)	(50)	(50)
MYXOSARCOMA	1 (2%)		
LIPOMA	2 (4%)		
*MESENTERY	(50)	(50)	(50)
MYXOSARCOMA		1 (2%)	
LIPOMA	1 (2%)	1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
MYXOSARCOMA, METASTATIC	1 (2%)		
MESOTHELIOMA, NOS		1 (2%)	1 (2%)
MESOTHELIOMA, INVASIVE	1 (2%)		
MESOTHELIOMA, METASTATIC	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHə	6	26	27
MORIBUND SACRIFICE	8	4	12
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	35	14	8
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1	6	3
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	49	35	33
TOTAL PRIMARY TUMORS	127	77	95
TOTAL ANIMALS WITH BENIGN TUMORS	48	35	31
TOTAL BENIGN TUMORS	98	58	67
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	13	18
TOTAL MALIGNANT TUMORS	22	14	23
TOTAL ANIMALS WITH SECONDARY TUMORS#	5	3	4
TOTAL SECONDARY TUMORS	7	4	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	7	5	5
TOTAL UNCERTAIN TUMORS	7	5	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

ə INCLUDES AUTOLYZED ANIMALS

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

TABLE A2.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL TUMOR		1 (2%)	
FIBROMA		1 (2%)	3 (6%)
FIBROSARCOMA	2 (4%)		2 (4%)
LEIOMYOSARCOMA			1 (2%)
RHABDOMYOSARCOMA			1 (2%)
FIBROADENOMA	2 (4%)	4 (8%)	2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
MONOCYTIC LEUKEMIA	20 (40%)	7 (14%)	2 (4%)
#SPLEEN	(50)	(50)	(47)
MONOCYTIC LEUKEMIA	1 (2%)		
#LUNG	(50)	(50)	(49)
MONOCYTIC LEUKEMIA			1 (2%)
#LIVER	(50)	(50)	(48)
MONOCYTIC LEUKEMIA			1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(30)	(31)	(28)
THYMOMA		1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CA, INVASIV		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(48)
NEOPLASTIC NODULE	3 (6%)	8 (16%)	8 (17%)
#PANCREAS	(50)	(49)	(47)
ACINAR-CELL ADENOMA			1 (2%)
ACINAR-CELL CARCINOMA			1 (2%)
#STOMACH	(50)	(49)	(45)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#DUODENUM	(50)	(46)	(43)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
ADENOMA, NOS	1 (2%)		
CHROMOPHOBE ADENOMA	25 (50%)	15 (31%)	16 (33%)
CHROMOPHOBE CARCINOMA	2 (4%)		
#ADRENAL	(50)	(50)	(48)
CORTICAL ADENOMA	2 (4%)	3 (6%)	5 (10%)
PHEOCHROMOCYTOMA	2 (4%)	5 (10%)	4 (8%)
#THYROID	(50)	(47)	(41)
FOLLICULAR-CELL CARCINOMA	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
C-CELL ADENOMA	7 (14%)		2 (5%)
C-CELL CARCINOMA	1 (2%)	4 (9%)	1 (2%)
#PARATHYROID	(31)	(38)	(31)
ADENOMA, NOS	1 (3%)		
#PANCREATIC ISLETS	(50)	(49)	(47)
ISLET-CELL ADENOMA		6 (12%)	2 (4%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)	
PAPILLARY ADENOMA			1 (2%)
CYSTADENOMA, NOS		1 (2%)	1 (2%)
LIPOMA		1 (2%)	
FIBROADENOMA	15 (30%)	21 (42%)	18 (36%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	1 (2%)		
ADENOMA, NOS		4 (8%)	
*VAGINA	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
ADENOMATOUS POLYP, NOS			1 (2%)
#UTERUS	(50)	(50)	(47)
ADENOCARCINOMA, NOS	1 (2%)		
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP	12 (24%)	9 (18%)	8 (17%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#OVARY/PAROVARIAN	(49)	(50)	(48)
LIPOMA	1 (2%)		
NERVOUS SYSTEM			
#PONS	(50)	(50)	(49)
CHROMOPHOBE CARCINOMA, METASTATI	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV		1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOMA		1 (2%)	
*MESENTERY	(50)	(50)	(50)
LIPOMA	2 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, UNC PRIM OR META			1 (2%)
PERIORBITAL REGION			
FIBROMA		1	
NECK			
C-CELL CARCINOMA, INVASIVE		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	19	31
MORIBUND SACRIFICE	6	7	13
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	36	19	5
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS		5	1
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	45	36	34
TOTAL PRIMARY TUMORS	106	99	87
TOTAL ANIMALS WITH BENIGN TUMORS	40	33	33
TOTAL BENIGN TUMORS	71	77	66
TOTAL ANIMALS WITH MALIGNANT TUMORS	28	13	11
TOTAL MALIGNANT TUMORS	32	14	12
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	
TOTAL SECONDARY TUMORS	2	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	8	8
TOTAL UNCERTAIN TUMORS	3	8	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			1

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: VEHICLE CONTROL

ANIMAL NUMBER	0012	0023	0034	0055	0066	0077	0088	0091	0101	0111	0122	0133	0144	0155	0166	0177	0188	0199	0200	0211	0222	0233	0244	0255
WEEKS ON STUDY	108	108	108	108	108	096	095	097	108	087	103	108	108	102	108	108	108	108	108	108	108	108	101	108
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																					X			
TRICHOEPITHELIOMA																						X		
KERATOACANTHOMA							X																	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR				X																				
ADENOCARCINOMA, NOS																								X
SARCOMA, NOS							X																	
FIBROMA											X								X					
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOM.			X																					
ALVEOLAR/BRONCHIOLAR CARCINOMA																					X			
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	-	-	+	+	+	-	+	+	+	+	-	+	+	-	+	+	-	-
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																					X			
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE							X								X		X		X			X		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																								
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
MESOTHELIOMA, METASTATIC											X													
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																								
LIPOMA																								
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS													X											
CHROMOPHOBE ADENOMA																								
CHROMOPHOBE CARCINOMA																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL CARCINOMA									X															
PHEOCHROMOCYTOMA				X							X					X	X							X
GANGLIONEUROMA									X															
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
C-CELL ADENOMA																								
C-CELL CARCINOMA																								
PARATHYROID	+	+	+	+	-	+	-	+	+	+	-	+	+	-	+	+	+	+	-	+	+	-	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																			X					
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	N	+	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	N
FIBROADENOMA																			X		X	X		
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
MESOTHELIOMA, MALIGNANT													X											
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	+	-	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS	X															X				X				X
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																								
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																								
CARTILAGE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA										X														
BODY CAVITIES																								
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																					X			
THYMOMA																	X							
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MYXOSARCOMA																								
LIPOMA																								
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA																								
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS, METASTATIC																								X
MYXOSARCOMA, METASTATIC																								
MESOTHELIOMA, INVASIVE																								
MESOTHELIOMA, METASTATIC																								
MONOCYTIC LEUKEMIA					X		X			X	X						X	X					X	

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

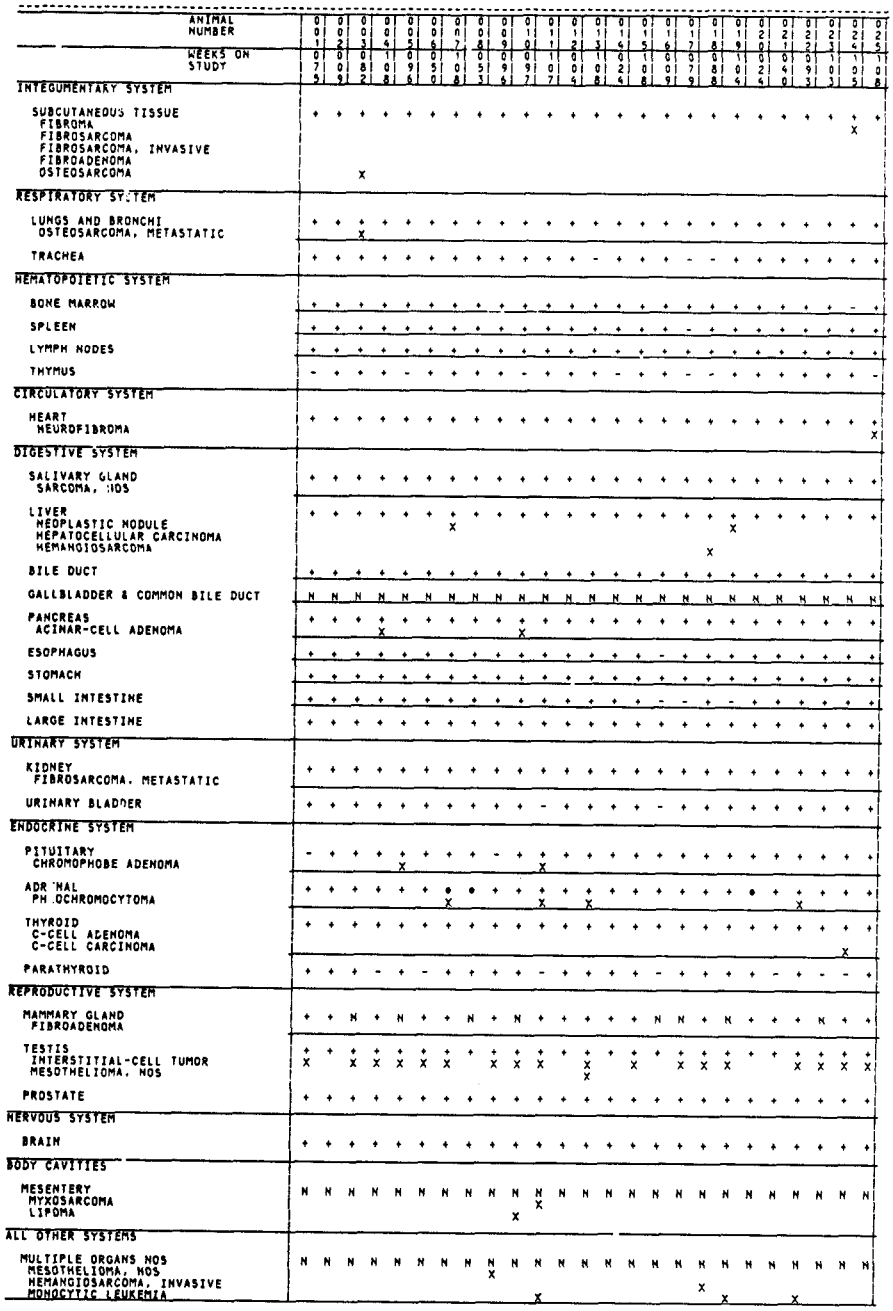
TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	0212 06	0212 07	0212 08	0212 09	0313 00	0313 11	0313 12	0313 13	0313 14	0313 15	0313 16	0313 17	0313 18	0313 19	0414 00	0414 11	0414 12	0414 13	0414 14	0414 15	0414 16	0414 17	0414 18	0414 19	0500	TOTAL TISSUES TUMORS
WEEKS ON STUDY	01 7 9	01 0 8	01 9 6	01 8 8	01 0 0	01 8 8	01 0 8	01 0 8	01 0 8	01 8 8	01 0 8	01 0 8	01 0 8	01 1 8	01 0 9	01 1 8	01 0 8	01 1 8	01 0 8	01 0 8	01 1 8	01 0 8	01 0 8	01 0 8	01 1 6	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
TRICHOEPITHELIOMA																										1
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	+	50
BASAL-CELL TUMOR																										1
ADENOCARCINOMA, NOS																										1
SARCOMA, NOS																										1
FIBROMA																	X									3
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	-	+	+	+	-	+	+	-	+	-	+	+	-	-	+	+	+	+	-	+		37
HEMATOPOIETIC SYSTEM																										
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
THYMUS	-	+	-	+	+	-	-	-	-	-	+	+	+	+	-	-	+	-	+	+	-	-	+	-		27
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NEOPLASTIC NODULE		X																					X			7
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+		47
ACINAR-CELL ADENOMA													X													1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+		49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
MESOTHELIOMA, METASTATIC																										1
SMALL INTESTINE	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+		46
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ADENOCARCINOMA, NOS		X																								1
LIPOMA													X													1
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+		44
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ADENOMA NOS											X															2
CHROMOPHOBE ADENOMA		X											X							X						3
CHROMOPHOBE CARCINOMA																	X									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
CORTICAL CARCINOMA																										1
PHEOCHROMOCYTOMA								X			X	X		X			X		X					X		12
GANGLIONEUROMA																										1
THYROID	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+		46
C-CELL ADENOMA								X																X		2
C-CELL CARCINOMA																	X									1
PARATHYROID	+	+	+	-	-	+	+	+	+	+	+	-	-	+	+	+	-	-	-	+	+	+	-	-		34
PANCREATIC ISLETS	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+		47
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
FIBROADENOMA										X			X										X	X		7
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		48
MESOTHELIOMA, MALIGNANT																								X		2
PROSTATE	+	+	•	-	+	+	+	+	+	+	+	•	•	+	•	+	•	+	+	+	•	+	+	+		44
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
ADENOMA, NOS		X			X														X							7
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
MUSCULOSKELETAL SYSTEM																										
MUSCLE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N		50
FIBROSARCOMA																	X									1
CARTILAGE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
LIPOMA																										1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																										1
THYMOMA																										1
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N		50
MYXOSARCOMA																	X									1
LIPOMA											X			X												2
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
LIPOMA				X																						1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50
ADENOCARCINOMA, NOS, METASTATIC																										1
MYXOSARCOMA, METASTATIC																	X									1
MESOTHELIOMA, INVASIVE																								X		1
MESOTHELIOMA, METASTATIC																								X		1
MONOCYTIC LEUKEMIA	X	X								X											X					11

M ANIMALS NECROPSIED

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: LOW DOSE



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

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

ANIMAL NUMBER / WEEKS ON STUDY	02 6 10	02 7 11	02 8 05	02 9 08	03 0 01	03 1 06	03 2 08	03 3 00	03 3 08	03 4 06	03 5 05	03 6 07	03 7 07	03 8 05	03 9 08	04 0 08	04 1 09	04 2 11	04 3 09	04 4 08	04 4 05	04 6 04	04 7 04	04 8 08	04 9 08	05 0 08	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																								X		X	3
FIBROSARCOMA	X	X																			X						3
FIBROSARCOMA, INVASIVE		X																									1
FIBROADENOMA									X																		1
OSTEOSARCOMA																											1
RESPIRATORY SYSTEM																											
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OSTEOSARCOMA, METASTATIC																											1
TRACHEA	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	-	+	+	+	+	+	41
HEMATOPOIETIC SYSTEM																											
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	-	+	+	+	+	+	+	+	+	47
THYMUS	+	+	+	+	+	+	+	+	+	-	+	-	-	+	+	-	-	+	+	+	+	+	+	-	+	+	37
CIRCULATORY SYSTEM																											
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEUROFIBROMA																											1
DIGESTIVE SYSTEM																											
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS														X													1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																											2
HEPATOCELLULAR CARCINOMA															X												1
HEMANGIOSARCOMA																											1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	+	+	47
ACINAR-CELL ADENOMA		X																									1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	-	-	-	+	+	+	-	-	+	+	+	-	+	-	+	+	+	39
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	47
URINARY SYSTEM																											
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+		48
FIBROSARCOMA, METASTATIC		X																									1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		47
ENDOCRINE SYSTEM																											
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	+	44
CHROMOPHOBE ADENOMA										X				X													4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
PHEOCHROMOCYTOMA		X																		X	X						7
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
C-CELL ADENOMA				X																	X						2
C-CELL CARCINOMA									X																		2
PARATHYROID	+	+	+	+	-	-	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	-	+	+	-		36
REPRODUCTIVE SYSTEM																											
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	X	+	+	N	+	+	50M
FIBROADENOMA																											1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X		X	X	X	X	X	X	X		X	X				X	X	X			X		X	35
MESOTHELIOMA, NOS									X																		2
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																											
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																											
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MYXOSARCOMA																											1
LIPOMA																											1
ALL OTHER SYSTEMS																											
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MESOTHELIOMA, NOS																											1
HEMANGIOSARCOMA, INVASIVE																											1
MONOCYTIC LEUKEMIA																										X	4

M ANIMALS NECROPSIED

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

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: HIGH DOSE

ANIMAL NUMBER	0012	0023	0041	0052	0066	0077	0081	0091	0103	0114	0124	0136	0146	0155	0166	0174	0188	0198	0210	0221	0236	0244	0255
WEEKS ON STUDY	052	000	078	008	008	070	038	042	047	041	008	010	026	055	044	084	038	051	018	096	024	068	073
INTEGUMENTARY SYSTEM																							
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS																							
SQUAMOUS CELL CARCINOMA																							
KERATOACANTHOMA									X														
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA			X						X														
FIBROSARCOMA																				X			
MESOTHELIOMA, INVASIVE																							
NEURILEMOMA, MALIGNANT																							
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	-	-	+	-	+	+	-	+	+	+	-	+	+	+	-	+	+	-	-	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+
THYMUS	-	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	-	+	+	+	-	+	-
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																							
HEPATOCELLULAR CARCINOMA																			X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA				X					X											X			
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+
STOMACH	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA, METASTATIC																				X			
NEPHROBLASTOMA																							
URINARY BLADDER	+	+	-	-	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA				X											X								
CHROMOPHOBE CARCINOMA																							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA			X					X															
PHEOCHROMOCYTOMA, MALIGNANT																			X				
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA								X															
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	-	-	+
ADENOMA, NOS																			X				
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA									X														
ISLET-CELL CARCINOMA																							X
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	+	+	N	N	+	+	+	+
FIBROADENOMA																X	X						
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR			X	X		X	X	X	X							X	X			X	X		X
INTERSTITIAL-CELL TUMOR, MALIGNAN																							
MESOTHELIOMA, MALIGNANT																							
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																							
NERVOUS SYSTEM																							
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE CARCINOMA, INVASIVE																							
PINEALOMA																				X			
GLIOMA, NOS																	X				X		
SPECIAL SENSE ORGANS																							
EAR	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N
SQUAMOUS CELL CARCINOMA																							
BODY CAVITIES																							
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
INTERSTITIAL-CELL TUMOR, METASTAT																							
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																							X
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																							
MONOCYTIC LEUKEMIA			X											X									

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

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

ANIMAL NUMBER	0216	0227	0238	0249	0301	0311	0312	0313	0314	0315	0316	0317	0318	0319	0401	0412	0423	0434	0445	0456	0467	0478	0489	0501	TOTAL
WEEKS ON STUDY	1018	0916	0714	0151	1122	0821	0921	0818	0816	0719	0818	0813	0818	1121	0202	0241	0490	0901	0818	0831	0990	0990	0831	0812	0610	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
PAPILLOMA, NOS	X																								1
SQUAMOUS CELL CARCINOMA																								X	1
KERATOACANTHUMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA	X			X		X				X			X									X		X	9
FIBROSARCOMA									X											X					3
MESOTHELIOMA, INVASIVE									X																1
NEURILEMOMA, MALIGNANT		X																							1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	36
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
THYMUS	+	+	+	-	+	+	+	+	-	-	+	-	+	+	+	+	+	+	+	-	+	+	+	-	36
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																		X		X					2
HEPATOCELLULAR CARCINOMA				X																					2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA	X					X			X				X												1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA, METASTATIC																									1
NEPHROBLASTOMA											X														1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	44
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CHROMOPHOBE ADENOMA		X									X	X						X		X					7
CHROMOPHOBE CARCINOMA												X													1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA				X					X		X									X					6
PHEOCHROMOCYTOMA, MALIGNANT																									1
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
C-CELL CARCINOMA											X														2
PARATHYROID	+	-	+	+	-	-	-	-	+	-	-	+	-	-	+	+	+	+	+	+	-	+	+	-	33
ADENOMA, NOS																									1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																				X					2
ISLET-CELL CARCINOMA																									2
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	N	+	+	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	50*
FIBROADENOMA												X													3
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR		X	X	X		X	X		X	X	X	X	X					X	X	X	X	X		X	29
INTERSTITIAL-CELL TUMOR, MALIGNAN	X																								1
MESOTHELIOMA, MALIGNANT									X																1
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS												X													1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHROMOPHOBE CARCINOMA, INVASIVE												X													1
PINEALOMA																									1
GLIOMA, NOS																									2
SPECIAL SENSE ORGANS																									
EAR	N	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	50*
SQUAMOUS CELL CARCINOMA		X																							1
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
INTERSTITIAL-CELL TUMOR, METASTAT	X							-																	1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	50*
MESOTHELIOMA, NOS																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MESOTHELIOMA, NOS										X															1
MONOCYTIC LEUKEMIA							X											X							4

* ANIMALS NECROPSIED

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

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

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	108	071	096	096	089	081	108	081	081	066	081	108	108	081	083	081	121	081	079	081	081	081	081	081	108
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA					X	X																			
FIBROADENOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA												X													
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MONOCYTIC LEUKEMIA																									
LYMPH NODES	+	,	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+
THYMUS	+	-	-	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X	X			X					X			X	X		X			X	X		X	
CHROMOPHOBE ADENOMA																			X						
CHROMOPHOBE CARCINOMA																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA								X																	
PHEOCHROMOCYTOMA													X												
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA								X					X	X					X			X			
C-CELL CARCINOMA																									
PARATHYROID	-	+	-	+	+	-	-	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	-	+
ADENOMA, NOS																	X								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA			X											X	X								X		
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																				X					
ENDOMETRIAL STROMAL POLYP			X	X			X			X								X		X					
ENDOMETRIAL STROMAL SARCOMA					X																				
OVARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	\	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE CARCINOMA, METASTATIC																									
BODY CAVITIES																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA		X																							
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, METASTATIC																									
MALIGNANT LYMPHOMA, NOS																									
MONOCYTIC LEUKEMIA				X				X			X		X			X	X							X	

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

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	108	107	108	108	103	108	108	108	108	108	108	108	108	108	108	108	108	109	108	108	108	104	107	108	108	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROSARCOMA		X																								2
FIBROADENOMA																				X						2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	45
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MONOCYTIC LEUKEMIA																										
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	45
THYMUS	-	-	-	+	+	-	-	+	+	+	+	-	-	-	+	+	-	+	+	+	-	-	+	-	-	30
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE										X					X								X			3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	^	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																									X	1
CHROMOPHOBE ADENOMA			X	X		X			X	X		X		X	X	X				X	X	X	X	X	X	25
CHROMOPHOBE CARCINOMA																	X									2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA							X																			2
PHEOCHROMOCYTOMA		X																								2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA					X																					1
C-CELL ADENOMA							X													X						7
C-CELL CARCINOMA												X														1
PARATHYROID	-	+	-	+	-	+	+	-	+	-	-	-	+	+	+	-	+	+	-	-	+	-	+	+	+	31
ADENOMA, NOS																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROADENOMA			X				X		X			X		X	X	X	X		X			X		X		15
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS		X																								1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
ENDOMETRIAL STROMAL POLYP	X		X	X														X						X	X	12
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIPOMA														X												1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CHROMOPHOBE CARCINOMA, METASTATIC																	X									1
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
LIPOMA						X																				2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FIBROSARCOMA, METASTATIC		X																								1
MALIGNANT LYMPHOMA, NOS					X																					1
MONOCYTIC LEUKEMIA	X	X							X	X		X	X			X		X	X	X		X	X	X		28

M ANIMALS NECROPSIED

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

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

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	071	108	008	084	106	108	108	111	108	088	103	088	005	006	108	051	108	051	108	024	058	070	108	108	108
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BASAL-CELL TUMOR																									
FIBROMA																									
FIBROADENOMA					X														X						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA										X															
TRACHEA	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	-	+	-	-	-	-	-	+	+	+	-	-	+	+	-	-	-	-	+	+	-
THYMOMA						X																			
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CA, INVASIVE										X															
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE		X			X						X				X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
STOMACH	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA		X							X			X			X		X				X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA											X														
PHEOCHROMOCYTOMA		X									X				X									X	
THYROID	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA																					X				
PARATHYROID	-	+	+	-	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA											X				X				X						
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	
ADENOMA, NOS												X													
CYSTADENOMA, NOS																			X						
LIPOMA																									X
FIBROADENOMA		X		X			X				X	X								X		X		X	X
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																					N				
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP		X				X			X		X	X								X					X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
PLEURA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, INVASIVE										X															
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA					X						X														
PERIORBITAL REGION																			X						
FIBROMA																									
NECK NOS																									
C-CELL CARCINOMA, INVASIVE																									

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

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

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

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50*
PAPILLOMA, NOS	1
SUBCUTANEOUS TISSUE	50*
BASAL-CELL TUMOR	1
FIBROMA	1
FIBROADENOMA	4
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
ALVEOLAR/BRONCHIOLAR ADENOMA	1
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
TRACHEA	38
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
SPLEEN	50
LYMPH NODES	47
THYMUS	31
THYMOMA	1
CIRCULATORY SYSTEM	
HEART	50
ALVEOLAR/BRONCHIOLAR CA, INVASIVE	1
DIGESTIVE SYSTEM	
SALIVARY GLAND	49
LIVER	50
NEOPLASTIC NODULE	A
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50*
PANCREAS	49
ESOPHAGUS	49
STOMACH	49
SMALL INTESTINE	46
ADENOCARCINOMA, NOS	1
LARGE INTESTINE	50
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	48
ENDOCRINE SYSTEM	
PITUITARY	49
CHROMOPHOBE ADENOMA	15
ADRENAL	50
CORTICAL ADENOMA	3
PHEOCHROMOCYTOMA	5
THYROID	47
C-CELL CARCINOMA	4
PARATHYROID	38
PANCREATIC ISLETS	49
ISLET-CELL ADENOMA	6
ISLET-CELL CARCINOMA	1
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50*
ADENOMA, NOS	1
CYSTADENOMA, NOS	1
LIPOMA	1
FIBROADENOMA	21
PREPUTIAL/CLITORAL GLAND	50*
ADENOMA, NOS	4
UTERUS	50
ENDOMETRIAL STROMAL POLYP	9
OVARY	50
NERVOUS SYSTEM	
BRAIN	50
BODY CAVITIES	
PLEURA	50*
ALVEOLAR/BRONCHIOLAR CA, INVASIVE	1
PERITONEUM	50*
LIPOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50*
MONOCYTIC LEUKEMIA	7
PERIORBITAL REGION	
FIBROMA	1
NECK NOS	
C-CELL CARCINOMA, INVASIVE	1

* ANIMALS NECROPSIED

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

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036
WEEKS ON STUDY	108	123	129	135	150	109	121	115	144	082	144	102	096	097	117	079	124	104	080	121	118	080	116	086	069
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA								X																X	
FIBROSARCOMA																					X				
LEIOMYOSARCOMA																									
RHABDOMYOSARCOMA									X																
FIBROADENOMA																		X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
MONOCYTIC LEUKEMIA													X												
TRACHEA	+	-	+	+	+	-	+	+	+	-	+	+	+	+	-	+	-	+	+	-	+	+	-	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LYMPH NODES	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+
THYMUS	-	+	-	-	+	+	+	+	+	+	-	-	-	-	+	+	-	+	-	+	-	+	-	+	+
CIRCULATORY SYSTEM																									
HEART	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
LIVER	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE	X																								
MONOCYTIC LEUKEMIA																		X				X			
BILE DUCT	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ACINAR-CELL CARCINOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	-	+	+	-	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA			X					X				X			X				X					X	
ADRENAL	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA	X																					X		X	
PHEOCHROMOCYTOMA				X											X							X			
THYROID	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+
C-CELL ADENOMA				X																					
C-CELL CARCINOMA																									
PARATHYROID	-	+	-	+	+	-	+	+	+	-	+	-	+	-	+	-	+	+	-	-	+	+	+	+	-
PANCREATIC ISLETS	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ISLET-CELL ADENOMA	X																								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY ADENOMA																									
CYSTADENOMA, NOS																									
FIBROADENOMA	X		X	X				X					X	X										X	
VAGINA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA																									
ADENOMATOUS POLYP, NOS											X														
UTERUS	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																									
ENDOMETRIAL STROMAL POLYP			X				X				X										X				
OVARY	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA, UNC PRIM OR META																			X						
MONOCYTIC LEUKEMIA	X																								

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

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

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES / TUMORS
INTEGUMENTARY SYSTEM	
SUBCUTANEOUS TISSUE	50 50
FIBROMA	5
FIBROSARCOMA	2
LEIOMYOSARCOMA	1
RHABDOMYOSARCOMA	1
FIBROADENOMA	2
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	49
ALVEOLAR/BRONCHIOLAR ADENOMA	1
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
MONOCYTIC LEUKEMIA	1
TRACHEA	31
HEMATOPOIETIC SYSTEM	
BONE MARROW	49
SPLEEN	47
LYMPH NODES	45
THYMUS	28
CIRCULATORY SYSTEM	
HEART	49
DIGESTIVE SYSTEM	
SALIVARY GLAND	45
LIVER	48
NEOPLASTIC NODULE	8
MONOCYTIC LEUKEMIA	1
BILE DUCT	48
GALLBLADDER & COMMON BILE DUCT	50 50
PANCREAS	47
ACINAR-CELL ADENOMA	1
ACINAR-CELL CARCINOMA	1
ESOPHAGUS	50
STOMACH	45
SMALL INTESTINE	43
LARGE INTESTINE	42
URINARY SYSTEM	
KIDNEY	48
URINARY BLADDER	44
ENDOCRINE SYSTEM	
PITUITARY	49
CHROMOPHOBE ADENOMA	16
ADRENAL	48
CORTICAL ADENOMA	5
PHEOCHROMOCYTOMA	1
THYROID	41
C-CELL ADENOMA	2
C-CELL CARCINOMA	1
PARATHYROID	31
PANCREATIC ISLETS	47
ISLET-CELL ADENOMA	2
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50 50
PAPILLARY ADENOMA	1
CYSTADENOMA, NOS	1
FIBROADENOMA	14
VAGINA	50 50
SQUAMOUS CELL PAPILLOMA	1
ADENOMATOUS POLYP, NOS	1
UTERUS	47
LEIOMYOSARCOMA	1
ENDOMETRIAL STROMAL POLYP	8
OVARY	48
NERVOUS SYSTEM	
BRAIN	49
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50 50
OSTEOSARCOMA, UNC PRIM OR META	1
MONOCYTIC LEUKEMIA	2

M ANIMALS NECROPSIED

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

APPENDIX B

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

TABLE B1.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
FIBROMA	2 (4%)		
FIBROSARCOMA		4 (8%)	
NEUROFIBROMA		1 (2%)	
*SUBCUT TISSUE	(50)	(49)	(50)
SARCOMA, NOS	1 (2%)		
FIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(48)	(49)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	3 (6%)	2 (4%)	2 (4%)
#SPLEEN	(48)	(47)	(49)
MALIGNANT LYMPHOMA, NOS		2 (4%)	
#MEDIASTINAL L.NODE	(41)	(35)	(37)
ALVEOLAR/BRONCHIOLAR CA, METASTA	1 (2%)		
#MESENTERIC L. NODE	(41)	(35)	(37)
MALIGNANT LYMPHOMA, NOS	2 (5%)		
#LIVER	(49)	(48)	(50)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#DUODENUM	(46)	(44)	(37)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#JEJUNUM	(46)	(44)	(37)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*EPIDIDYMIS	(50)	(49)	(50)
HEMANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(49)	(48)	(50)
HEPATOCELLULAR ADENOMA	5 (10%)	3 (6%)	2 (4%)
HEPATOCELLULAR CARCINOMA	6 (12%)	9 (19%)	3 (6%)
#FORESTOMACH	(48)	(47)	(50)
PAPILLOMA, NOS	1 (2%)		
#DUODENUM	(46)	(44)	(37)
PAPILLOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(42)	(41)
ADENOMA, NOS		1 (2%)	
#ADRENAL	(49)	(48)	(50)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
#THYROID	(46)	(39)	(44)
FOLLICULAR-CELL ADENOMA		1 (3%)	1 (2%)
#PANCREATIC ISLETS	(49)	(47)	(50)
ISLET-CELL CARCINOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#TESTIS	(49)	(49)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS	2 (4%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
FIBROSARCOMA, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	4	8	20
MORIBUND SACRIFICE		1	4
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	46	40	26
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED		1	
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	22	27	9
TOTAL PRIMARY TUMORS	29	33	11
TOTAL ANIMALS WITH BENIGN TUMORS	11	11	4
TOTAL BENIGN TUMORS	13	12	5
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	19	6
TOTAL MALIGNANT TUMORS	16	21	6
TOTAL ANIMALS WITH SECONDARY TUMORS#	3	2	
TOTAL SECONDARY TUMORS	3	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)	1 (2%)
MYXOSARCOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	
SARCOMA, NOS, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC	4 (8%)		1 (2%)
OSTEOSARCOMA, UNC PRIM OR META			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	9 (18%)	14 (28%)	12 (24%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)
LEUKEMIA,NOS	3 (6%)		
#MEDIASTINAL L.NODE	(45)	(44)	(44)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
OSTEOSARCOMA, METASTATIC			1 (2%)
OSTEOSARCOMA, UNC PRIM OR META			1 (2%)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(45)	(44)	(44)
MALIGNANT LYMPHOMA, NOS		2 (5%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#INGUINAL LYMPH NODE	(45)	(44)	(44)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#JEJUNUM	(45)	(50)	(41)
MALIGNANT LYMPHOMA, NOS		1 (2%)	
#THYMUS	(38)	(34)	(40)
MALIGNANT LYMPHOMA, NOS			1 (3%)
CIRCULATORY SYSTEM			
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOMA			2 (4%)
#SPLEEN	(50)	(50)	(49)
HEMANGIOMA		1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
#OVARY	(47)	(47)	(48)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	3 (6%)	12 (24%)
HEPATOCELLULAR CARCINOMA	2 (4%)	2 (4%)	3 (6%)
SARCOMA, NOS, METASTATIC	1 (2%)		
#DUODENUM	(45)	(50)	(41)
PAPILLARY ADENOMA			1 (2%)
#CECUM	(45)	(50)	(46)
LEIOMYOSARCOMA	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC	1 (2%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(43)
ADENOMA, NOS	4 (9%)	3 (7%)	1 (2%)
#ADRENAL	(47)	(49)	(49)
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(44)	(44)	(48)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)
CARCINOSARCOMA		1 (2%)	
#UTERUS	(50)	(50)	(50)
LEIOMYOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		2 (4%)	
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		
#OVARY	(47)	(47)	(48)
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		1 (2%)
*VERTEBRAL COLUMN	(50)	(50)	(50)
OSTEOSARCOMA	2 (4%)		

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*RIB	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	5	17
MORIBUND SACRIFICE	4	2	
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	34	43	33
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS	1		
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			

@ INCLUDES AUTOLYZED ANIMALS

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	26	31	30
TOTAL PRIMARY TUMORS	30	36	48
TOTAL ANIMALS WITH BENIGN TUMORS	7	11	15
TOTAL BENIGN TUMORS	8	13	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	21	22
TOTAL MALIGNANT TUMORS	22	23	26
TOTAL ANIMALS WITH SECONDARY TUMORS#	6	2	1
TOTAL SECONDARY TUMORS	9	2	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			2

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	117	117	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA							X	X																	
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																									
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																					X				
ALVEOLAR/BRONCHIOLAR ADENOMA														X											
ALVEOLAR/BRONCHIOLAR CARCINOMA																X									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CA, METASTAT																	X								
MALIGNANT LYMPHOMA, NOS				X																					
THYMUS	+	-	+	+	+	-	+	+	-	-	+	-	+	+	+	+	+	-	-	+	-	+	+	+	•
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X									X										
HEPATOCELLULAR CARCINOMA								X											X		X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS																									
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS			X																						X
MALIGNANT LYMPHOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA						X																			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
EPIDIDYMIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																	X								
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS					X																				

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

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

ANIMAL NUMBER / WEEKS ON STUDY	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50M
FIBROMA	2
SUBCUTANEOUS TISSUE	50M
SARCOMA, NOS	1
FIBROSARCOMA	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
HEPATOCELLULAR CARCINOMA, METASTA	2
ALVEOLAR/BRONCHIOLAR ADENOMA	1
ALVEOLAR/BRONCHIOLAR CARCINOMA	1
TRACHEA	48
HEMATOPOIETIC SYSTEM	
BONE MARROW	45
SPLEEN	48
LYMPH NODES	41
ALVEOLAR/BRONCHIOLAR CA, METASTAT	1
MALIGNANT LYMPHOMA, NOS	2
THYMUS	37
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
SALIVARY GLAND	50
LIVER	49
HEPATOCELLULAR ADENOMA	5
HEPATOCELLULAR CARCINOMA	4
BILE DUCT	49
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	49
ESOPHAGUS	48
STOMACH	48
PAPILLOMA, NOS	1
SMALL INTESTINE	46
PAPILLOMA, NOS	1
MALIGNANT LYMPHOMA, NOS	1
LARGE INTESTINE	48
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	46
ENDOCRINE SYSTEM	
PITUITARY	46
ADRENAL	49
CORTICAL ADENOMA	1
THYROID	46
PARATHYROID	18
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
TESTIS	49
PROSTATE	49
EPIDIDYMIS	50M
HEMANGIOSARCOMA	1
NERVOUS SYSTEM	
BRAIN	50
SPECIAL SENSE ORGANS	
HARDERIAN GLAND	50M
ADENOMA, NOS	2
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
MALIGNANT LYMPHOMA, NOS	1

M ANIMALS NECROPSIED

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	093	107	107	107	107	093	107	107	107	107	095	096	107	073	097	107
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA									X												X			X	
NEUROFIBROMA																					X				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	-
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA										X						X									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	-	+	+	+	+	-
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	-	+	-	+	+	+	+	+	-	-	+	+	S	-	+	+	+	-	+	+	+	+	-
THYMUS	+	+	+	+	+	-	+	+	-	+	+	+	+	+	S	+	+	+	+	-	-	+	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																X									
HEPATOCELLULAR CARCINOMA	X																		X				X		
BILE DUCT	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	+	N	+	+	+	+	S	+	+	+	+	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	-	-	+
MALIGNANT LYMPHOMA, NOS					X																				
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	-	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA												X													
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	-	-	+	-	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA														X											
THYROID	-	-	-	+	-	+	+	+	+	+	+	+	+	+	S	+	+	+	+	-	+	+	+	+	-
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	-	-	-	+	-	+	-	+	-	-	+	-	S	-	+	+	-	-	-	-	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA		X																							
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR								X																	
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	S	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, METASTATIC																								X	
MALIGNANT LYMPHOMA, NOS																									

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

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

ANIMAL NUMBER	021 6	022 7	028 8	029 9	030 7	031 7	032 7	033 7	034 7	035 7	036 7	037 2	038 7	039 7	040 7	041 7	042 7	043 9	044 7	045 7	046 7	047 7	048 7	049 7	051 7	TOTAL TISSUES TUMORS
WEEKS ON STUDY	092	107	107	107	107	107	107	107	107	107	012	107	107	107	107	107	092	107	107	107	107	107	107	058	107	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
FIBROSARCOMA																								X		4
NEUROFIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR CARCINOMA, METASTA	X																									1
ALVEOLAR/BRONCHIOLAR ADENOMA							X			X									X							3
ALVEOLAR/BRONCHIOLAR CARCINOMA																										2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	47
MALIGNANT LYMPHOMA, NOS					X														X							2
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	-	-	-	+	+	-	-	+	+	+	+	+	-	+	35
THYMUS	+	+	+	-	-	-	+	+	+	+	-	+	+	-	+	-	-	+	+	+	+	+	+	+	+	35
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	48
HEPATOCELLULAR ADENOMA																							X			3
HEPATOCELLULAR CARCINOMA	X			X	X												X	X					X			9
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	49*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ESOPHAGUS	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
MALIGNANT LYMPHOMA, NOS																										1
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	42
ADENOMA, NOS			X																							1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CORTICAL ADENOMA																										1
THYROID	+	-	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	39
FOLLICULAR-CELL ADENOMA																			X							1
PARATHYROID	+	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	11
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
ISLET-CELL CARCINOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
FIBROSARCOMA, METASTATIC													X						X							1
MALIGNANT LYMPHOMA, NOS																										2

* ANIMALS NECROPSIED

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: HIGH DOSE

ANIMAL NUMBER	01 01 11	01 02 12	01 03 13	01 04 14	01 05 15	01 06 16	01 07 17	01 08 18	01 09 19	01 10 20	01 11 01	01 12 02	01 13 03	01 14 04	01 15 05	01 16 06	01 17 07	01 18 08	01 19 09	01 20 10	02 21 11	02 22 12	02 23 13	02 24 14	02 25 15
WEEKS ON STUDY	07 75	08 11	09 17	07 78	10 17	10 17	11 17	10 11	10 14	01 17	11 17	10 17	10 17	10 15	10 17	10 14	10 17	11 17	10 18	10 24	10 23	09 17	10 17	10 17	10 14
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA										X															
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
LYMPH NODES	+	-	+	-	+	-	+	-	+	-	+	+	+	-	+	-	+	+	-	-	+	+	+	-	-
THYMUS	-	-	+	+	+	+	-	+	+	-	+	+	+	-	-	-	+	+	+	-	+	+	+	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X																							
HEPATOCELLULAR CARCINOMA																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X								
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	N	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-	-	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	•	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	-
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS							X							X											

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	107	107	107	111	107	107	078	071	094	071	071	071	055	055	107	094	097	070	041	050	025	084	084	071	107	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	*	+	+	+	+	+	+	+	*	+	+	+	+	+	+	+	+	+	+	+	+	-	+	*	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA	X																									2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	*	+	+	+	+	+	+	+	+	*	+	+	+	+	+	+	*	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	37
THYMUS	-	+	+	+	+	-	+	-	+	+	+	-	-	+	-	-	-	+	+	+	-	-	+	+	-	28
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X	X																								2
HEPATOCELLULAR CARCINOMA													X	X												3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	N	+	+	N	+	N	N	N	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	-	+	+	-	+	-	+	+	+	-	-	+	-	+	+	-	+	-	-	+	+	+	37
LARGE INTESTINE	+	+	+	-	+	+	+	+	+	+	+	+	+	(	+	+	+	+	-	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	-	+	+	41
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	44
FOLLICULAR-CELL ADENOMA														X												1
PARATHYROID	-	+	-	-	-	-	-	-	-	+	-	-	-	+	-	+	-	+	+	+	+	-	-	+	+	16
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIGNANT LYMPHOMA, NOS																										2

* ANIMALS NECROPSIED

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

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	107	102	107	107	096	076	107	107	107	071	077	107	093	107	102	107	107	107	107	107	101	089	107	107	107
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METASTA SARCOMA, NOS, METASTATIC OSTEOSARCOMA, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+
TRACHEA	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES MALIG.LYMPHOMA, HISTIOCYTIC TYPE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
THYMUS	+	-	+	+	-	-	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA SARCOMA, NOS, METASTATIC	+	+	+	+	X	+	X	+	X	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+
LARGE INTESTINE LEIOMYOSARCOMA	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY OSTEOSARCOMA, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	-	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
THYROID FOLLICULAR-CELL ADENOMA	+	-	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+
PARATHYROID	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	+	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	N
UTERUS ENDOMETRIAL STROMAL SARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
NERVOUS SYSTEM																									
BRAIN	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MUSCULOSKELETAL SYSTEM																									
BONE OSTEOSARCOMA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
BODY CAVITIES																									
MEDIASTINUM OSTEOSARCOMA, METASTATIC	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS						X				X		X					X		X						
LEUKEMIA,NOS		X																			X				

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

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

ANIMAL NUMBER	02616	02717	02818	02909	03101	03211	03312	03413	03514	03616	03701	03808	03907	04004	04101	04201	04307	04407	04507	04607	04707	04807	04907	05010	TOTAL
WEEKS ON STUDY	10107	10107	10107	10807	10107	10107	10107	10507	10107	10107	10111	10807	10107	10407	10107	10107	10707	10107	10107	10107	10107	10111	10907	10107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	50* 1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METASTA																	X								1
SARCOMA, NOS, METASTATIC																									1
OSTEOSARCOMA, METASTATIC				X				X						X									X		4
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	45
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																							X		1
THYMUS	+	+	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	38
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	46
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																									2
HEPATOCELLULAR CARCINOMA																	X								2
SARCOMA, NOS, METASTATIC																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	N	+	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-	45
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	-	45
LEIOMYOSARCOMA																									1
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OSTEOSARCOMA, METASTATIC				X																					1
URINARY BLADDER	+	+	+	+	+	+	+	-	+	+	+	+	+	-	-	-	-	+	+	+	+	+	-	+	44
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	46
ADENOMA, NOS			X		X																				4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	44
FOLLICULAR-CELL ADENOMA																									1
PARATHYROID	-	-	+	+	+	+	-	+	-	-	+	+	+	-	-	-	+	-	-	+	-	-	-	+	16
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	50*
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL SARCOMA																									1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	48
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS													X												1
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA				X				X							X								X		4
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA, METASTATIC								X																	1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	X	N	N	X	N	N	N	N	N	N	X	N	N	N	X	50* 9
MALIGNANT LYMPHOMA, NOS													X												3
LEUKEMIA,NOS																									

* ANIMALS NECROPSIED

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

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

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	0 7 8	0 1 1	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	0 2 1	1 0 7	1 0 7
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																			X						
LYMPH NODES	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+
ALVEOLAR/BRONCHIOLAR CA, METASTAT																									
MALIGNANT LYMPHOMA, NOS		X																							
THYMUS	+	+	-	+	+	+	+	+	+	-	+	-	+	-	-	-	-	+	-	-	+	+	+	-	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA	X													X											
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	N	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS										X															
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	-	+	-	
ADENOMA, NOS					X													X							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																	X								
THYROID	-	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	-	+	+	+	
FOLLICULAR-CELL ADENOMA																		X							
PARATHYROID	-	+	+	+	-	+	-	-	+	-	-	+	-	+	-	+	+	+	-	-	+	-	-	-	
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	·	N	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+
CARCINOSARCOMA																								X	
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP																									X
OVARY	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, METASTATIC						X							X							X	X				
MALIGNANT LYMPHOMA, NOS																									

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

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	50
FIBROSARCOMA																					X				1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA													X						X						1
ALVEOLAR/BRONCHIOLAR CARCINOMA																									2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																									1
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ALVEOLAR/BRONCHIOLAR CA, METASTATIC													X												1
MALIGNANT LYMPHOMA, NOS														X											2
THYMUS	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-	+	+	+	-	+	-	34
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA							X																		3
HEPATOCELLULAR CARCINOMA										X														X	2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIGNANT LYMPHOMA, NOS																									1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	46
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
ADENOMA, NOS	X																								3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	49
PHEOCHROMOCYTOMA																									1
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	44
FOLLICULAR-CELL ADENOMA																									1
PARATHYROID	-	-	-	-	+	+	+	+	+	-	-	-	-	-	-	+	-	-	+	+	-	-	+	-	19
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	N	+	+	+	+	+	50
CARCINOSARCOMA																									1
UTERUS	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP														X											2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ADENOMA, NOS														X											1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
FIBROSARCOMA, METASTATIC																					X				1
MALIGNANT LYMPHOMA, NOS		X		X		X	X	X		X		X								X			X	X	14

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

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

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF TOLUENE DIISOCYANATE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	089	107	107	099	093	099	107	107	107	107	107	107	107	107	107	107	001	085	107	107	107	107	107	107	107
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA									X																
MYXOSARCOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA				X																					
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																							X		
OSTEOSARCOMA, METASTATIC						X																			
OSTEOSARCOMA, UNC PRIM OR META							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LYMPH NODES	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OSTEOSARCOMA, METASTATIC						X																			
OSTEOSARCOMA, UNC PRIM OR META							X																		
MALIGNANT LYMPHOMA, NOS																									X
THYMUS	-	+	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS													X												
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA								X	X	X	X											X		X	
HEPATOCELLULAR CARCINOMA																									
HEMANGIOSARCOMA																		X							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
STOMACH	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
PAPILLARY ADENOMA							X																		
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+
ADENOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	-	+	+	-	-	-	+	-	-	-	-	+	-	+	-	+	+	+	-	-	-	-	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+
ADENOCARCINOMA, NOS																		X							
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOMA						X																			
OVARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TERATOMA, NOS																						X			
HEMANGIOSARCOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
MUSCULOSKELETAL SYSTEM																									
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA						X																			
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS	X	X	X	X				X							X										
MALIG LYMPHOMA, HISTIOCYTIC TYPE																								X	

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

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

ANIMAL NUMBER	02216	02217	02218	02219	02310	02311	02312	02313	02314	02315	02316	02317	02318	02319	02320	02321	02322	02323	02324	02325	02326	02327	02328	02329	02330	TOTAL
WEEKS ON STUDY	03101	03201	03401	03701	03701	03701	04601	04601	04702	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	05001	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROSARCOMA																										1
MYXOSARCOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	50*
HEMANGIOMA																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
OSTEOSARCOMA, METASTATIC																										1
OSTEOSARCOMA, UNC PRIM OR META																										1
TRACHEA	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	44
OSTEOSARCOMA, METASTATIC																										1
OSTEOSARCOMA, UNC PRIM OR META																										1
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	+	+	+	-	+	+	-	+	+	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	40
MALIGNANT LYMPHOMA, NOS																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	X	X	+	X	+	+	+	X	50
HEPATOCELLULAR ADENOMA																										12
HEPATOCELLULAR CARCINOMA			X		X																				X	3
HEMANGIOSARCOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	+	+	N	+	+	+	N	N	+	+	+	+	+	N	N	+	+	+	N	N	+	+	+	+	50*
PANCREAS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
SMALL INTESTINE	-	-	+	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	41
PAPILLARY ADENOMA																										1
LARGE INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	-	+	+	+	X	+	+	+	+	+	+	+	-	+	+	+	-	43
ADENOMA, NOS																										1
ADRENAL	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
PARATHYROID	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	+	-	-	-	13
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
TERATOMA, NOS																										1
HEMANGIOSARCOMA				X																						1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS																			X							1
MUSCULOSKELETAL SYSTEM																										
BONE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
OSTEOSARCOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEMANGIOSARCOMA					X																					1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	X	N	N	N	N	N	N	X	N	N	N	X	N	N	N	N	X	N	N	50*
MALIGNANT LYMPHOMA, NOS																									X	12
MALIG LYMPHOMA, HISTIOCYTIC TYPE				X																						2

* ANIMALS NECROPSIED

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

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

APPENDIX C

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

TABLE C1.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
HEMORRHAGE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
HYPERKERATOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
RESPIRATORY SYSTEM			
*NASAL MUCOSA	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
*LARYNX	(50)	(50)	(50)
ULTIMOBRANCHIAL CYST		1 (2%)	
HEMORRHAGE		1 (2%)	
*LARYNGEAL GLAND	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
#TRACHEA	(37)	(41)	(36)
INFLAMMATION, ACUTE		3 (7%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#LUNG/BRONCHUS	(50)	(50)	(50)
BRONCHIECTASIS		1 (2%)	
#LUNG	(50)	(50)	(50)
MINERALIZATION	2 (4%)	1 (2%)	
CONGESTION, NOS	3 (6%)		2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
EDEMA, NOS	2 (4%)	12 (24%)	4 (8%)
HEMORRHAGE	4 (8%)	1 (2%)	3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	6 (12%)	5 (10%)
PNEUMONIA, ASPIRATION			1 (2%)
BRONCHOPNEUMONIA, ACUTE	2 (4%)	6 (12%)	14 (28%)
INFLAMMATION, ACUTE	2 (4%)	2 (4%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
PNEUMONIA, CHRONIC MURINE		1 (2%)	
BRONCHOPNEUMONIA, CHRONIC		1 (2%)	
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, NOS	1 (2%)	1 (2%)	2 (4%)
CHOLESTEROL DEPOSIT			1 (2%)
FOREIGN MATERIAL, NOS		2 (4%)	2 (4%)
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HISTIOCYTOSIS	13 (26%)	9 (18%)	9 (18%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HEMATOPOIESIS	4 (8%)	1 (2%)	2 (4%)
#BONE MARROW	(49)	(49)	(47)
MYELOFIBROSIS	4 (8%)	3 (6%)	1 (2%)
#SPLEEN	(49)	(48)	(49)
CONGESTION, NOS			1 (2%)
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, NOS			1 (2%)
HEMOSIDEROSIS	8 (16%)	8 (17%)	5 (10%)
LYMPHOID DEPLETION		1 (2%)	
HEMATOPOIESIS	5 (10%)	2 (4%)	
#SPLENIC CAPSULE	(49)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
SIDEROPHAGOCYTOSIS	1 (2%)		
#SPLENIC RED PULP	(49)	(48)	(49)
COLLAPSE	2 (4%)		1 (2%)
#LYMPH NODE	(48)	(47)	(43)
EDEMA, NOS			1 (2%)
PLASMACYTOSIS			1 (2%)
#MANDIBULAR L. NODE	(48)	(47)	(43)
DILATATION, NOS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS		1 (2%)	
EDEMA, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	4 (9%)
INFLAMMATION, ACUTE			1 (2%)
PLASMACYTOSIS	22 (46%)	18 (38%)	14 (33%)
#MEDIASTINAL L.NODE	(48)	(47)	(43)
HEMORRHAGE	12 (25%)	7 (15%)	5 (12%)
HISTIOCYTOSIS	1 (2%)		
PLASMACYTOSIS	1 (2%)		1 (2%)
#MESENTERIC L. NODE	(48)	(47)	(43)
DILATATION, NOS			1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#RENAL LYMPH NODE	(48)	(47)	(43)
HEMORRHAGE		1 (2%)	
#STOMACH	(49)	(49)	(47)
SIDEROPHAGOCYTOSIS	1 (2%)		
#COLON	(48)	(47)	(44)
HYPERPLASIA, LYMPHOID	1 (2%)		
#ADRENAL	(50)	(49)	(50)
HEMATOPOIESIS	3 (6%)	1 (2%)	1 (2%)
#THYMUS	(27)	(37)	(36)
CYST, NOS	2 (7%)		3 (8%)
HEMORRHAGE		3 (8%)	1 (3%)
NECROSIS, CORTICAL			1 (3%)
LYMPHOID DEPLETION		1 (3%)	2 (6%)
CIRCULATORY SYSTEM			
#BRAIN	(50)	(49)	(50)
THROMBOSIS, NOS	1 (2%)		
#LUNG	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#HEART	(50)	(50)	(50)
MINERALIZATION	2 (4%)		
THROMBOSIS, NOS	2 (4%)	1 (2%)	1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMORRHAGE		2 (4%)	3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	3 (6%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	3 (6%)
FIBROSIS	46 (92%)	34 (68%)	31 (62%)
FIBROSIS, FOCAL	1 (2%)		
*CORONARY ARTERY	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION	14 (28%)		5 (10%)
#ADRENAL	(50)	(49)	(50)
THROMBOSIS, NOS			2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(48)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
FIBROSIS			1 (2%)
ATROPHY, NOS	2 (4%)	2 (4%)	6 (13%)
#LIVER	(50)	(50)	(50)
ABNORMAL CURVATURE	2 (4%)	1 (2%)	3 (6%)
CYST, NOS			1 (2%)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, ACUTE		2 (4%)	3 (6%)
GRANULOMA, NOS	4 (8%)	2 (4%)	1 (2%)
DEGENERATION, CYSTIC		1 (2%)	6 (12%)
NECROSIS, NOS	7 (14%)	3 (6%)	5 (10%)
NECROSIS, CENTRAL	1 (2%)		
CYTOPLASMIC VACUOLIZATION	3 (6%)	1 (2%)	5 (10%)
BASOPHILIC CYTO CHANGE	42 (84%)	32 (64%)	33 (66%)
EOSINOPHILIC CYTO CHANGE	17 (34%)	28 (56%)	21 (42%)
ATYPIA, NOS	4 (8%)	1 (2%)	1 (2%)
ANGIECTASIS	1 (2%)		
#LIVER/KUPFFER CELL	(50)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	45 (90%)	30 (60%)	28 (56%)
#PANCREAS	(47)	(47)	(49)
ACCESSORY STRUCTURE			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)
ATROPHY, NOS	2 (4%)		
#PANCREATIC ACINUS	(47)	(47)	(49)
CYST, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
ATROPHY, NOS	10 (21%)	6 (13%)	6 (12%)
ATROPHY, EXHAUSTION		1 (2%)	
HYPERPLASIA, NODULAR		2 (4%)	4 (8%)
#PERIPANCREATIC TISSU	(47)	(47)	(49)
NECROSIS, FAT			1 (2%)
#ESOPHAGUS	(49)	(48)	(47)
INFLAMMATION, CHRONIC		1 (2%)	
#STOMACH	(49)	(49)	(47)
MINERALIZATION	1 (2%)		
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION, ACUTE	14 (29%)	9 (18%)	7 (15%)
ULCER, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
FIBROSIS			1 (2%)
HYPERPLASIA, EPITHELIAL	5 (10%)	1 (2%)	
#GASTRIC FUNDAL GLAND	(49)	(49)	(47)
DILATATION, NOS	1 (2%)		
#JEJUNUM	(46)	(39)	(44)
ECTOPIA	1 (2%)	1 (3%)	1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
#COLON	(48)	(47)	(44)
HEMORRHAGE	1 (2%)		
PARASITISM	1 (2%)	1 (2%)	4 (9%)
*RECTUM	(50)	(50)	(50)
POLYP, INFLAMMATORY		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(49)
MINERALIZATION	3 (6%)	1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYDRONEPHROSIS	2 (4%)		
CONGESTION, NOS	6 (12%)	1 (2%)	1 (2%)
HEMORRHAGE	1 (2%)		
GLOMERULONEPHRITIS, NOS	1 (2%)		
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
NEPHROPATHY	48 (96%)	38 (79%)	35 (71%)
PIGMENTATION, NOS	2 (4%)	2 (4%)	
HISTIOCYTOSIS			1 (2%)
#KIDNEY/PELVIS	(50)	(48)	(49)
HYPERPLASIA, EPITHELIAL			1 (2%)
#URINARY BLADDER	(44)	(47)	(44)
EDEMA, NOS	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (5%)	1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		
ULCER, ACUTE HEMORRHAGIC	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(44)	(49)
CYST, NOS	6 (12%)	4 (9%)	7 (14%)
HYPERPLASIA, CHROMOPHOBE-CELL	12 (24%)	3 (7%)	3 (6%)
ANGIECTASIS		1 (2%)	
#ADRENAL	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	3 (6%)
INFLAMMATION, ACUTE		1 (2%)	
CYTOPLASMIC VACUOLIZATION	3 (6%)	3 (6%)	
ANGIECTASIS	1 (2%)	1 (2%)	
#ADRENAL CORTEX	(50)	(49)	(50)
CYTOPLASMIC CHANGE, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	4 (8%)	1 (2%)	4 (8%)
HYPERPLASIA, NODULAR	8 (16%)	8 (16%)	
#ADRENAL MEDULLA	(50)	(49)	(50)
HYPERPLASIA, NOS	8 (16%)	3 (6%)	3 (6%)
#THYROID	(46)	(49)	(47)
ULTIMOBRANCHIAL CYST		1 (2%)	2 (4%)
MINERALIZATION	2 (4%)	1 (2%)	2 (4%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
FOLLICULAR CYST, NOS	6 (13%)	4 (8%)	2 (4%)
HYPERPLASIA, C-CELL	15 (33%)	4 (8%)	2 (4%)
#PARATHYROID	(34)	(36)	(33)
HYPERPLASIA, NOS	12 (35%)	9 (25%)	4 (12%)
#PANCREATIC ISLETS	(47)	(47)	(49)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	2 (4%)	2 (4%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, NOS	3 (6%)		
HYPERPLASIA, EPITHELIAL	3 (6%)		2 (4%)
LACTATION	2 (4%)	1 (2%)	3 (6%)
*PENIS	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
#PROSTATE	(44)	(50)	(47)
INFLAMMATION, ACUTE	1 (2%)	5 (10%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC	4 (9%)	5 (10%)	2 (4%)
INFLAMMATION, CHRONIC	4 (9%)	1 (2%)	1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		1 (2%)
FIBROSIS		1 (2%)	
HYPERPLASIA, EPITHELIAL	5 (11%)	2 (4%)	4 (9%)
METAPLASIA, SQUAMOUS			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#TESTIS	(50)	(50)	(50)
MINERALIZATION	25 (50%)	17 (34%)	21 (42%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, NOS		1 (2%)	
NECROSIS, FAT	1 (2%)		
ATYPIA, NOS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, INTERSTITIAL CELL		1 (2%)	3 (6%)
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)	
FIBROSIS	1 (2%)		1 (2%)
NERVOUS SYSTEM			
*CHOROID PLEXUS	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
#BRAIN	(50)	(49)	(50)
MINERALIZATION			1 (2%)
EDEMA, NOS		1 (2%)	1 (2%)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
GLIOSIS	2 (4%)		
MALACIA	1 (2%)		
ANGIECTASIS	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY	4 (8%)		1 (2%)
CATARACT	4 (8%)		2 (4%)
*SCLERA	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*CORNEA SUBSTANTIA PR	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
*EAR	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	4 (8%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PERITONEAL CAVITY	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
NECROSIS, FAT	1 (2%)		
*MESENTERY	(50)	(50)	(50)
HEMATOMA, NOS	1 (2%)		
INFLAMMATION, CALC GRANULOMATOUS		1 (2%)	
NECROSIS, FAT	2 (4%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	8 (16%)	24 (48%)	26 (52%)
HEMORRHAGE	1 (2%)		2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE	1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
FIBROSIS			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST			1 (2%)
ACANTHOSIS			1 (2%)
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
#TRACHEA	(45)	(38)	(31)
INFLAMMATION, ACUTE		1 (3%)	1 (3%)
#LUNG	(50)	(50)	(49)
MINERALIZATION		2 (4%)	1 (2%)
VEGETABLE FOREIGN BODY			1 (2%)
CONGESTION, NOS		2 (4%)	1 (2%)
EDEMA, NOS		7 (14%)	7 (14%)
HEMORRHAGE	3 (6%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, INTERSTITIAL			1 (2%)
BRONCHOPNEUMONIA, ACUTE	1 (2%)	10 (20%)	25 (51%)
INFLAMMATION, ACUTE			4 (8%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
GRANULOMA, NOS	1 (2%)	2 (4%)	1 (2%)
FIBROSIS			2 (4%)
FOREIGN MATERIAL, NOS		5 (10%)	1 (2%)
PIGMENTATION, NOS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	2 (4%)	5 (10%)
HISTIOCYTOSIS	13 (26%)	14 (28%)	6 (12%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PLASMACYTOSIS		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS		4 (8%)	9 (18%)
#BONE MARROW	(49)	(49)	(49)
OSTEOSCLEROSIS		1 (2%)	
MYELOFIBROSIS		4 (8%)	5 (10%)
#SPLEEN	(50)	(50)	(47)
GRANULOMA, NOS			1 (2%)
FIBROSIS			1 (2%)
HEMOSIDEROSIS	24 (48%)	14 (28%)	15 (32%)
LYMPHOID DEPLETION	1 (2%)		2 (4%)
HEMATOPOIESIS	1 (2%)	6 (12%)	2 (4%)
#LYMPH NODE	(45)	(47)	(45)
PLASMACYTOSIS			1 (2%)
#MANDIBULAR L. NODE	(45)	(47)	(45)
HEMORRHAGE	1 (2%)		1 (2%)
GRANULOMA, NOS		1 (2%)	
NECROSIS, NOS	1 (2%)		
ATROPHY, NOS			1 (2%)
PLASMACYTOSIS	23 (51%)	19 (40%)	16 (36%)
#MEDIASTINAL L.NODE	(45)	(47)	(45)
HEMORRHAGE	5 (11%)	6 (13%)	7 (16%)
INFLAMMATION, ACUTE		1 (2%)	3 (7%)
GRANULOMA, NOS		1 (2%)	
PIGMENTATION, NOS	1 (2%)		
PLASMACYTOSIS	2 (4%)	2 (4%)	2 (4%)
#PANCREATIC L.NODE	(45)	(47)	(45)
EDEMA, NOS	1 (2%)		
#RENAL LYMPH NODE	(45)	(47)	(45)
HEMORRHAGE		2 (4%)	
#LIVER	(50)	(50)	(48)
LEUKEMOID REACTION			1 (2%)
HEMATOPOIESIS			2 (4%)
#THYMUS	(30)	(31)	(28)
CYST, NOS	3 (10%)	2 (6%)	2 (7%)
HEMORRHAGE		1 (3%)	1 (4%)
NECROSIS, CORTICAL		1 (3%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
#HEART	(50)	(50)	(49)
THROMBOSIS, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE		2 (4%)	1 (2%)
FIBROSIS	37 (74%)	29 (58%)	30 (61%)
*PULMONARY ARTERY	(50)	(50)	(50)
MINERALIZATION	4 (8%)	2 (4%)	
*SPLENIC ARTERY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
#LIVER	(50)	(50)	(48)
THROMBOSIS, NOS	2 (4%)		1 (2%)
#UTERUS	(50)	(50)	(47)
THROMBOSIS, NOS	1 (2%)		
#ADRENAL	(50)	(50)	(48)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(49)	(45)
FIBROSIS			1 (2%)
ATROPHY, NOS		3 (6%)	7 (16%)
#LIVER	(50)	(50)	(48)
ABNORMAL CURVATURE	6 (12%)		3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE NECROTIZING			2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, GRANULOMATOUS		2 (4%)	
GRANULOMA, NOS	20 (40%)	4 (8%)	4 (8%)
FIBROSIS			1 (2%)
NECROSIS, NOS	4 (8%)	5 (10%)	3 (6%)
PIGMENTATION, NOS	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYTOPLASMIC VACUOLIZATION	2 (4%)	1 (2%)	2 (4%)
BASOPHILIC CYTO CHANGE	42 (84%)	37 (74%)	43 (90%)
EOSINOPHILIC CYTO CHANGE	12 (24%)	22 (44%)	31 (65%)
ATYPIA, NOS	2 (4%)	2 (4%)	
ANGIECTASIS		1 (2%)	
#BILE DUCT	(50)	(50)	(48)
HYPERPLASIA, NOS	26 (52%)	10 (20%)	3 (6%)
#PANCREAS	(50)	(49)	(47)
ACCESSORY STRUCTURE			1 (2%)
DILATATION/DUCTS	1 (2%)		
CYST, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
FIBROSIS	2 (4%)		
ATROPHY, NOS	1 (2%)		
#PANCREATIC ACINUS	(50)	(49)	(47)
CYTOPLASMIC VACUOLIZATION			1 (2%)
ATROPHY, NOS	6 (12%)	5 (10%)	2 (4%)
#ESOPHAGUS	(48)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
#STOMACH	(50)	(49)	(45)
CYST, NOS	1 (2%)		
EDEMA, NOS			1 (2%)
INFLAMMATION, NOS	1 (2%)		
INFLAMMATION, ACUTE	22 (44%)	7 (14%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, EPITHELIAL	7 (14%)		2 (4%)
#GASTRIC FUNDAL GLAND	(50)	(49)	(45)
DILATATION, NOS	1 (2%)	1 (2%)	1 (2%)
#JEJUNUM	(50)	(46)	(43)
ECTOPIA	1 (2%)	2 (4%)	
#COLON	(49)	(50)	(42)
PARASITISM		1 (2%)	2 (5%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(48)
MINERALIZATION	10 (20%)	3 (6%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CYST, NOS	1 (2%)		
CONGESTION, NOS	1 (2%)		
PYELONEPHRITIS, CHRONIC	1 (2%)		
NEPHROPATHY	34 (68%)	36 (72%)	40 (83%)
DEPOSIT, NOS	1 (2%)		
PIGMENTATION, NOS	4 (8%)	1 (2%)	
#PERIRENAL TISSUE	(50)	(50)	(48)
INFLAMMATION, CHRONIC			1 (2%)
#URINARY BLADDER	(48)	(48)	(44)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	2 (4%)	
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(49)
MINERALIZATION	1 (2%)		
CYST, NOS	22 (44%)	21 (43%)	15 (31%)
GRANULOMA, NOS	1 (2%)		
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	3 (6%)	4 (8%)	2 (4%)
ANGIECTASIS	2 (4%)		1 (2%)
#ADRENAL	(50)	(50)	(48)
CONGESTION, NOS	2 (4%)	2 (4%)	5 (10%)
DEGENERATION, CYSTIC			2 (4%)
NECROSIS, NOS		2 (4%)	
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	4 (8%)	1 (2%)
HYPERPLASIA, NODULAR		1 (2%)	2 (4%)
ANGIECTASIS		4 (8%)	1 (2%)
#ADRENAL/CAPSULE	(50)	(50)	(48)
FIBROSIS		1 (2%)	
#ADRENAL CORTEX	(50)	(50)	(48)
FIBROSIS		1 (2%)	
DEGENERATION, CYSTIC			1 (2%)
CYTOPLASMIC CHANGE, NOS			2 (4%)
CYTOPLASMIC VACUOLIZATION	6 (12%)	2 (4%)	4 (8%)
HYPERPLASIA, NODULAR	18 (36%)	14 (28%)	8 (17%)
HYPERPLASIA, FOCAL	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(48)
HYPERPLASIA, NOS	6 (12%)	4 (8%)	2 (4%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(50)	(47)	(41)
MINERALIZATION			1 (2%)
FOLLICULAR CYST, NOS	10 (20%)	3 (6%)	
HYPERPLASIA, C-CELL	11 (22%)	12 (26%)	4 (10%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#THYROGLOSSAL DUCT	(50)	(47)	(41)
ULTIMOBRANCHIAL CYST			1 (2%)
#PARATHYROID	(31)	(38)	(31)
HYPERPLASIA, NOS	4 (13%)	7 (18%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	7 (14%)	10 (20%)	4 (8%)
GALACTOCELE		1 (2%)	2 (4%)
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, EPITHELIAL	2 (4%)	3 (6%)	
HYPERPLASIA, CYSTIC		1 (2%)	
LACTATION	14 (28%)	10 (20%)	9 (18%)
*CLITORAL GLAND	(50)	(50)	(50)
IMPACTION, NOS			1 (2%)
*VAGINA	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING			1 (2%)
#UTERUS	(50)	(50)	(47)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE			1 (2%)
NECROSIS, FAT			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(47)
CYST, NOS	7 (14%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
#FALLOPIAN TUBE	(50)	(50)	(47)
INFLAMMATION, ACUTE		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#OVARY/PAROVARIAN	(49)	(50)	(48)
NECROSIS, FAT	1 (2%)	1 (2%)	
#OVARY	(49)	(50)	(48)
CYST, NOS	3 (6%)	1 (2%)	4 (8%)
FOLLICULAR CYST, NOS	1 (2%)		
NECROSIS, NOS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(49)
MINERALIZATION	1 (2%)		1 (2%)
HYDROCEPHALUS, NOS	1 (2%)		
EDEMA, NOS	2 (4%)	1 (2%)	1 (2%)
HEMORRHAGE	2 (4%)	1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
RETINOPATHY	5 (10%)	4 (8%)	2 (4%)
CATARACT	3 (6%)	5 (10%)	
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
OSTEOSCLEROSIS			1 (2%)
*CARTILAGE,NOS	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, ACUTE			2 (4%)
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
NECROSIS, FAT	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MINERALIZATION	2 (4%)		
CONGESTION, NOS	3 (6%)	19 (38%)	29 (58%)
INFLAMMATION, ACUTE			1 (2%)
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	1		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

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

TABLE D1.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
FIBROSIS	1 (2%)		
RESPIRATORY SYSTEM			
*LARYNX	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#TRACHEA	(48)	(46)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)	3 (6%)
#LUNG/BRONCHUS	(50)	(48)	(49)
BRONCHIECTASIS			1 (2%)
#LUNG	(50)	(48)	(49)
CONGESTION, NOS			1 (2%)
HEMORRHAGE	9 (18%)	8 (17%)	8 (16%)
BRONCHOPNEUMONIA, NOS	1 (2%)		5 (10%)
INFLAMMATION, INTERSTITIAL	16 (32%)	12 (25%)	17 (35%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
BRONCHOPNEUMONIA, CHRONIC		1 (2%)	1 (2%)
PERIVASCULAR CUFFING	1 (2%)		
EPITHELIALIZATION		1 (2%)	
#LUNG/ALVEOLI	(50)	(48)	(49)
HISTIOCYTOSIS		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(43)	(47)	(48)
NECROSIS, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
MYELOFIBROSIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#SPLEEN	(48)	(47)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)	3 (6%)	1 (2%)
HEMATOPOIESIS		2 (4%)	
#LYMPH NODE	(41)	(35)	(37)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#MANDIBULAR L. NODE	(41)	(35)	(37)
HYPERPLASIA, LYMPHOID		1 (3%)	
#MEDIASTINAL L.NODE	(41)	(35)	(37)
PLASMACYTOSIS		1 (3%)	1 (3%)
HYPERPLASIA, LYMPHOID		1 (3%)	1 (3%)
#MESENTERIC L. NODE	(41)	(35)	(37)
HEMORRHAGE	5 (12%)	2 (6%)	
#RENAL LYMPH NODE	(41)	(35)	(37)
PLASMACYTOSIS			1 (3%)
#LIVER	(49)	(48)	(50)
HEMATOPOIESIS		1 (2%)	
#ILEUM	(46)	(44)	(37)
HYPERPLASIA, LYMPHOID	2 (4%)		
#THYMUS	(37)	(35)	(28)
CYST, NOS	1 (3%)		2 (7%)
HYPERPLASIA, LYMPHOID			1 (4%)
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
POLYANGIITIS		1 (2%)	
#MYOCARDIUM	(50)	(49)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CARDIAC VALVE	(50)	(49)	(49)
PIGMENTATION, NOS	1 (2%)		
*BLOOD VESSEL	(50)	(49)	(50)
POLYANGIITIS		1 (2%)	
*VAS DEFERENS	(50)	(49)	(50)
POLYANGIITIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	4 (8%)	1 (2%)	1 (2%)
FIBROSIS		1 (2%)	
ATROPHY, NOS		1 (2%)	
#LIVER	(49)	(48)	(50)
TORSION	1 (2%)		
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, MULTIFOCAL	2 (4%)		1 (2%)
NECROSIS, COAGULATIVE	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	
GROUND-GLASS CYTO CHANGE	4 (8%)	2 (4%)	
ANGIECTASIS			1 (2%)
#PANCREAS	(49)	(47)	(50)
DILATATION/DUCTS		1 (2%)	
CYST, NOS		1 (2%)	1 (2%)
#PANCREATIC ACINUS	(49)	(47)	(50)
ATROPHY, NOS		2 (4%)	
#ESOPHAGUS	(48)	(46)	(47)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#STOMACH	(48)	(47)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
EROSION			1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#GASTRIC MUCOSA	(48)	(47)	(50)
CYST, NOS			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(48)	(50)
CALCULUS, NOS		1 (2%)	
MINERALIZATION	1 (2%)		
PYELONEPHRITIS, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	10 (20%)	4 (8%)	5 (10%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
NEPHROPATHY	1 (2%)	1 (2%)	
NECROSIS, NOS	1 (2%)		
CYTOMEGALY		45 (94%)	41 (82%)
HYPERPLASIA, TUBULAR CELL			1 (2%)
METAPLASIA, OSSEOUS	1 (2%)		
#KIDNEY/TUBULE	(50)	(48)	(50)
DEGENERATION, NOS		1 (2%)	
#URINARY BLADDER	(46)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (6%)
INFLAMMATION, CHRONIC		1 (2%)	
*URETHRA	(50)	(49)	(50)
HEMORRHAGE			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(42)	(41)
CYST, NOS		1 (2%)	
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	
#ADRENAL	(49)	(48)	(50)
MINERALIZATION		1 (2%)	
#ADRENAL CORTEX	(49)	(48)	(50)
FOCAL CELLULAR CHANGE	2 (4%)	2 (4%)	1 (2%)
#ADRENAL MEDULLA	(49)	(48)	(50)
FOCAL CELLULAR CHANGE		1 (2%)	
#THYROID	(46)	(39)	(44)
PERSISTENT EMBRYONIC STRUCTURE			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, FOCAL		1 (3%)	
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(49)	(50)
CONGESTION, NOS			1 (2%)
*PREPUTIAL GLAND	(50)	(49)	(50)
DILATATION/DUCTS		1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ABSCESS, NOS	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, NOS			2 (4%)
#PROSTATE	(49)	(49)	(47)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(49)	(49)	(50)
MINERALIZATION	19 (39%)	12 (24%)	4 (8%)
NECROSIS, NOS	1 (2%)		
HYPOSPERMATOGENESIS	1 (2%)	2 (4%)	4 (8%)
*EPIDIDYMIS	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
GRANULOMA, SPERMATIC			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
PIGMENTATION, NOS	2 (4%)	1 (2%)	
#BRAIN	(50)	(49)	(50)
CONGESTION, NOS			1 (2%)
HEMORRHAGE			1 (2%)
#BRAIN/THALAMUS	(50)	(49)	(50)
CALCULUS, NOS	16 (32%)	19 (39%)	12 (24%)
MINERALIZATION	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(50)
CATARACT			1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*EAR	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
NECROSIS, NOS	8 (16%)	5 (10%)	6 (12%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(49)	(50)
HEMORRHAGE	5 (10%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	34 (68%)	30 (61%)	26 (52%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1
ANIMAL MIS-SEXED/NO NECROPSY		1	

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

TABLE D2.

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

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#TRACHEA	(47)	(49)	(48)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
#LUNG/BRONCHUS	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
#LUNG	(49)	(50)	(50)
CONGESTION, NOS			1 (2%)
HEMORRHAGE	3 (6%)	4 (8%)	5 (10%)
BRONCHOPNEUMONIA, NOS		1 (2%)	4 (8%)
INFLAMMATION, INTERSTITIAL	16 (33%)	17 (34%)	18 (36%)
PNEUMONIA, ASPIRATION	1 (2%)		
INFLAMMATION, SUPPURATIVE			2 (4%)
PERIVASCULAR CUFFING		1 (2%)	
HEMOSIDEROSIS	1 (2%)		
#LUNG/ALVEOLI	(49)	(50)	(50)
HISTIOCYTOSIS		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(46)	(48)
MYELOFIBROSIS	41 (82%)	38 (83%)	32 (67%)
#SPLEEN	(50)	(50)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, LYMPHOID	1 (2%)		4 (8%)
HEMATOPOIESIS	3 (6%)	2 (4%)	2 (4%)
#LYMPH NODE	(45)	(44)	(44)
PLASMACYTOSIS	1 (2%)		
HEMATOPOIESIS	1 (2%)		
#MANDIBULAR L. NODE	(45)	(44)	(44)
HYPERPLASIA, LYMPHOID			1 (2%)
#MEDIASTINAL L.NODE	(45)	(44)	(44)
HEMORRHAGE	1 (2%)		
PLASMACYTOSIS			1 (2%)
#HEPATIC LYMPH NODE	(45)	(44)	(44)
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(45)	(44)	(44)
HEMORRHAGE	1 (2%)		
MASTOCYTOSIS			1 (2%)
#RENAL LYMPH NODE	(45)	(44)	(44)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (2%)
#SACRAL LYMPH NODE	(45)	(44)	(44)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
#INGUINAL LYMPH NODE	(45)	(44)	(44)
HYPERPLASIA, LYMPHOID		1 (2%)	
*STERNUM	(50)	(50)	(50)
MYELOFIBROSIS	1 (2%)		
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
HEMATOPOIESIS	1 (2%)		1 (2%)
#THYMUS	(38)	(34)	(40)
HYPERPLASIA, LYMPHOID	1 (3%)	1 (3%)	
CIRCULATORY SYSTEM			
#HEART	(49)	(50)	(50)
ARTERIOSCLEROSIS, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(49)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
#CARDIAC VALVE	(49)	(50)	(50)
PIGMENTATION, NOS	1 (2%)	2 (4%)	
*AORTA	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
#UTERUS	(50)	(50)	(50)
POLYANGIITIS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(46)	(48)	(47)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)
INFLAMMATION, ACUTE			1 (2%)
#LIVER	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, MULTIFOCAL	1 (2%)	1 (2%)	
FIBROSIS	1 (2%)		
NECROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
NECROSIS, COAGULATIVE	2 (4%)	1 (2%)	2 (4%)
METAMORPHOSIS FATTY			2 (4%)
CYTOPLASMIC VACUOLIZATION		2 (4%)	
BASOPHILIC CYTO CHANGE	1 (2%)	1 (2%)	2 (4%)
GROUND-GLASS CYTO CHANGE	3 (6%)		2 (4%)
EOSINOPHILIC CYTO CHANGE			1 (2%)
#PANCREAS	(49)	(50)	(48)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
#PANCREATIC ACINUS	(49)	(50)	(48)
ATROPHY, NOS	1 (2%)		1 (2%)
#ESOPHAGUS	(48)	(48)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
#STOMACH	(49)	(50)	(48)
ULCER, NOS	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS	1 (2%)		
GLOMERULONEPHRITIS, NOS	1 (2%)		1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	9 (18%)	1 (2%)	
METAMORPHOSIS FATTY			1 (2%)
METAPLASIA, OSSEOUS		1 (2%)	
#URINARY BLADDER	(44)	(46)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (14%)	1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(43)
CYST, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	
FOCAL CELLULAR CHANGE	3 (7%)	4 (9%)	4 (9%)
ANGIECTASIS		1 (2%)	
#ADRENAL	(47)	(49)	(49)
CONGESTION, NOS			1 (2%)
#ADRENAL CORTEX	(47)	(49)	(49)
FOCAL CELLULAR CHANGE		3 (6%)	2 (4%)
#ADRENAL MEDULLA	(47)	(49)	(49)
FOCAL CELLULAR CHANGE			1 (2%)
#THYROID	(44)	(44)	(48)
CYST, NOS		1 (2%)	
ATROPHY, FOCAL	10 (23%)	10 (23%)	9 (19%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		1 (2%)
#UTERUS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	42 (84%)	44 (88%)	33 (66%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#OVARY	(47)	(47)	(48)
MINERALIZATION	1 (2%)		
FOLLICULAR CYST, NOS	2 (4%)	2 (4%)	1 (2%)
PAROVARIAN CYST	7 (15%)	6 (13%)	9 (19%)
HEMORRHAGIC CYST	1 (2%)		1 (2%)
ABSCESS, NOS	1 (2%)		
ANGIECTASIS			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(48)	(50)	(50)
PIGMENTATION, NOS	1 (2%)	4 (8%)	
#BRAIN	(48)	(50)	(50)
HEMOSIDEROSIS	1 (2%)		
#BRAIN/THALAMUS	(48)	(50)	(50)
CALCULUS, NOS	16 (33%)	10 (20%)	11 (22%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		
CATARACT			1 (2%)
MUSCULOSKELETAL SYSTEM			
*STERNUM	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)	6 (12%)	3 (6%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
HEMATOMA, NOS		1 (2%)	
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
CYST, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	26 (52%)	34 (68%)	24 (48%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, CHRONIC	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

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

APPENDIX E

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE E1. HISTORICAL INCIDENCE OF SUBCUTANEOUS TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Skin Fibroma	Skin Fibrosarcoma	Subcutaneous Fibroma	Subcutaneous Fibrosarcoma
Battelle	0/100 (0.0%)	0/100 (0.0%)	6/100 (6.0%)	2/100 (2.0%)
Gulf South	0/294 (0.0%)	0/294 (0.0%)	12/294 (4.1%)	1/294 (0.3%)
Hazleton	0/50 (0.0%)	0/50 (0.0%)	2/50 (4.0%)	1/50 (2.0%)
Litton	0/130 (0.0%)	0/130 (0.0%)	5/130 (3.8%)	0/130 (0.0%)
Mason	0/125 (0.0%)	0/125 (0.0%)	10/125 (8.0%)	1/125 (0.8%)
Papanicolaou	0/50 (0.0%)	0/50 (0.0%)	4/50 (8.0%)	0/50 (0.0%)
Southern	0/250 (0.0%)	0/250 (0.0%)	16/250 (6.4%)	5/250 (2.0%)
Total	0/999 (0.0%)	0/999 (0.0%)	55/999 (5.5%)	10/999 (1.0%)
Overall Historical Range				
High	0/50	0/50	6/50	5/50
Low	0/50	0/50	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E2. HISTORICAL INCIDENCE OF SUBCUTANEOUS TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Skin Fibroma	Skin Fibrosarcoma	Subcutaneous Fibroma	Subcutaneous Fibrosarcoma
Battelle	0/100 (0.0%)	0/100 (0.0%)	0/100 (1.0%)	2/100 (2.0%)
Gulf South	0/295 (0.0%)	0/295 (0.0%)	4/295 (1.4%)	1/295 (0.3%)
Hazleton	0/50 (0.0%)	0/50 (0.0%)	3/50 (6.0%)	2/50 (4.0%)
Litton	0/130 (0.0%)	0/130 (0.0%)	0/130 (0.0%)	2/130 (1.5%)
Mason	0/124 (0.0%)	0/124 (0.0%)	0/124 (0.0%)	0/124 (0.0%)
Papanicolaou	0/50 (0.0%)	0/50 (0.0%)	1/50 (2.0%)	0/5 (0.0%)
Southern	2/250 (0.8%)	0/250 (0.0%)	1/250 (0.4%)	1/250 (0.4%)
Total	2/999 (0.2%)	0/999 (0.0%)	8/999 (0.8%)	8/999 (0.8%)
Overall Historical Range				
High	1/50	0/50	3/50	2/50
Low	0/50	0/50	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E3. HISTORICAL INCIDENCE OF FIBROMAS AND ADENOMAS OF THE MAMMARY GLAND AND SUBCUTANEOUS TISSUE IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Mammary Gland Fibroadenomas	Mammary Gland Tumors *(b)*	Subcutaneous Tissue Tumors *(c)*	Mammary or Subcutaneous *(b,c)*
Battelle	11 100 (11%)	15 100 (15.0%)	0 100 (0%)	15 100 (15.0%)
Gulf South	46 295 (15.6%)	55 295 (18.6%)	7 295 (2.4%)	62 295 (21.0%)
Hazleton	8 50 (16%)	9 50 (18.0%)	3 50 (6.0%)	12 50 (24.0%)
Litton	23 130 (17.7%)	23 130 (17.7%)	2 130 (1.5%)	25 130 (19.2%)
Mason	34 124 (27.4%)	36 124 (29.0%)	0 124 (0%)	36 124 (29.0%)
Papanicolaou	9 50 (18.0%)	9 50 (18.0%)	1 50 (2.0%)	10 50 (20.0%)
Southern	63 250 (25.2%)	65 250 (26.0%)	2 250 (0.8%)	67 250 (26.8%)
Total	194 999 (19.4%)	212 999 (21.2%)	15 999 (1.5%)	227 999 (22.7%)
Overall Historical Range				
High	18 50	18 50	4 50	18 50
Low	1 48	4 50	0 50	4 48

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.
(b) Mammary tumors include: fibroadenoma, adenoma, NOS, fibroma, papillary adenoma, cystadenoma, papillary cystadenoma.
(c) Subcutaneous tissue tumors include: fibroadenoma, fibroma.

TABLE E4. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Leukemia	Lymphoma	Lymphoma or Leukemia
Battelle	14/100 (14.0%)	4/100 (4.0%)	18/100 (18%)
Gulf South	29/294 (9.9%)	4/294 (1.4%)	31/294 (10.5%)
Hazleton	12/50 (24.0%)	2/50 (4.0%)	14/50 (28.0%)
Litton	13/130 (10.0%)	0/130 (0.0%)	13/130 (10.0%)
Mason	13/125 (10.4%)	2/125 (2.0%)	15/125 (12.0%)
Papanicolaou	5/50 (10.0%)	1/50 (2.0%)	6/50 (12.0%)
Southern	10/250 (4.0%)	1/250 (0.4%)	11/250 (4.4%)
Total	96/999 (9.6%)	14/999 (1.4%)	108/999 (10.8%)
Overall Historical Range			
High	12/50 (24%)	4/50 (1.4%)	14/50 (28.0%)
Low	1/50 (2.0%)	0/50 (0.0%)	1/50 (2.0%)

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E5. HISTORICAL INCIDENCE OF HEMATOPOIETIC TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Leukemia	Lymphoma	Lymphoma or Leukemia
Battelle	18/100 (18.0%)	3/100 (3.0%)	21/100 (21%)
Gulf South	30/295 (10.2%)	6/295 (2.0%)	36/295 (12.2%)
Hazleton	2/50 (4.0%)	1/50 (2.0%)	3/50 (6.0%)
Litton	28/130 (21.5%)	2/130 (1.5%)	30/130 (23.1%)
Mason	14/124 (11.3%)	1/124 (0.8%)	15/124 (12.1%)
Papanicolaou	14/50 (28.0%)	0/50 (0.0%)	14/50 (28.0%)
Southern	26/250 (10.4%)	2/250 (0.8%)	28/250 (11.2%)
Total	132/999 (13.2%)	15/999 (1.5%)	147/999 (14.7%)
Overall Historical Range			
High	21/50	3/49	22/50
Low	1/49	0/50	2/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E6. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL ADENOMAS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	
Battelle	0/100 (0%)
Gulf South	2/286 (0.7%)
Hazleton	0/49 (0%)
Litton	1/125 (0.8%)
Mason	1/121 (0.8%)
Papanicolaou	0/47 (0%)
Southern	2/248 (0.8%)
Total	6/976 (0.6%)
Overall Historical Range	
High	1/47
Low	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals. No acinar cell carcinomas have been observed in male rats receiving corn oil by gavage.

TABLE E7. HISTORICAL INCIDENCE OF PANCREATIC ISLET TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Islet Cell Adenoma	Islet Cell Carcinoma
Battelle	1/96 (1.0%)	1/96 (1.0%)
Gulf South	1/288 (0.3%)	0/288 (0.0%)
Hazleton	4/50 (8.0%)	0/50 (0.0%)
Litton	0/125 (0.0%)	0/125 (0.0%)
Mason	0/122 (0.0%)	0/122 (0.0%)
Papanicolaou	0/48 (0.0%)	0/48 (0.0%)
Southern	2/247 (0.8%)	0/247 (0.0%)
Total	8/976 (0.8%)	1/976 (0.1%)
Overall Historical Range		
High	4/50	1/50
Low	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E8. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Carcinoma
Battelle	1/99 (1.0%)	0/99 (0.0%)	1/99 (1.0%)
Gulf South	6/244 (2.5%)	1/244 (0.4%)	7/244 (2.9%)
Hazleton	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Litton	4/129 (3.1%)	0/129 (0.0%)	4/129 (3.1%)
Mason	2/124 (1.6%)	0/124 (0.0%)	2/124 (1.6%)
Papanicolaou	0/50 (0.0%)	0/50 (0.0%)	0/50 (0.0%)
Southern	1/250 (0.4%)	0/250 (0.0%)	1/250 (0.4%)
Total	14/946 (1.5%)	1/946 (0.1%)	15/946 (1.6%)
Overall Historical Range			
High	4/49	1/49	4/49
Low	0/50	0/50	0/50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E9. HISTORICAL INCIDENCE OF BRAIN TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Site	Diagnosis	
Battelle	Cerebrum	Astrocytoma	1/100 (1.0%)
Gulf South	Brain, NOS	Glioma	2/292 (0.7%)
	Medula Oblongata, NOS	Neuroma	1/292 (0.3%)
Hazleton			0/50 (0.0%)
Litton	Brain, NOS	Ependymoma	1/129 (0.8%)
Mason	Brain, NOS	Glioma	1/125 (0.8%)
	Cerebellum, NOS	Astrocytoma	1/125 (0.8%)
Papanicolaou			0/49 (0.0%)
Southern	Brain, NOS	Astrocytoma	3/250 *(b)* (1.2%)
Total incidence of all brain tumors			10/995 (1.0%)

(a) Data as of November 30, 1981 for studies of at least 104 weeks.
(b) Two astrocytomas were found in a group of 50.

TABLE E10. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Hemangioma		Hemangiosarcoma	
Battelle	1/99	(1.0%)	6/99	(6.1%)
Gulf South	2/341	(0.6%)	6/341	(1.8%)
Litton	1/119	(0.8%)	2/119	(1.7%)
Mason	1/150	(0.7%)	3/150	(2.0%)
Papanicolaou	1/48	(2.1%)	0/48	(0.0%)
Southern	1/250	(0.4%)	5/250	(2.0%)
Total	7/1007	(0.7%)	22/1007	(2.2%)
Overall Historical Range				
High	2/50		3/49	
Low	0/97		0/50	

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

TABLE E11. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

Laboratory	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Battelle	4 98 (4.1%)	3 98 (3.1%)	6 98 (6.1%)
Gulf South	15 334 (4.5%)	11 334 (3.3%)	26 334 (7.8%)
Litton	2 118 (1.7%)	3 118 (2.5%)	5 118 (4.2%)
Mason	8 148 (5.4%)	3 148 (2.0%)	11 148 (7.4%)
Papanicolaou	2 48 (4.2%)	2 48 (8.3%)	4 48 (8.3%)
Southern	7 250 (2.8%)	8 250 (3.2%)	15 250 (6.0%)
Total	38 996 (3.8%)	30 996 (3.0%)	67 996 (6.7%)
Overall Historical Range			
High	5 50	3 49	7 50
Low	0 50	0 49	1 50

(a) Data as of November 30, 1981 for studies of at least 104 weeks. The range is presented for groups of 35 or more animals.

APPENDIX F

ANALYSIS OF PRIMARY TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Control	30 mg/kg	60 mg/kg
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	3/50 (6%)	9/50 (18%)
Adjusted *(b)*	8.3%	16.5%	56.6%
Terminal *(c)*	3/36 (8%)	1/14 (7%)	3/8 (38%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.258	P<0.001
Incidental Tumor Test	P=0.002	P=0.415	P=0.004
Cochran-Armitage Trend Test	P=0.033		
Fisher Exact Test		P=0.661	P=0.061
Subcutaneous Tissue: Fibrosarcoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted *(b)*	0.0%	19.0%	23.1%
Terminal *(c)*	0/36 (0%)	2/14 (14%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.003	P=0.020	P=0.008
Incidental Tumor Test	P=0.021	P=0.044	P=0.089
Cochran-Armitage Trend Test	P=0.101		
Fisher Exact Test		P=0.121	P=0.121
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	6/50 (12%)	12/50 (24%)
Adjusted *(b)*	8.3%	33.5%	66.6%
Terminal *(c)*	3/36 (8%)	3/14 (21%)	3/8 (38%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.016	P<0.001
Incidental Tumor Test	P<0.001	P=0.056	P<0.001
Cochran-Armitage Trend Test	P=0.007		
Fisher Exact Test		P=0.243	P=0.011
Subcutaneous Tissue: All Sarcomas			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	3/50 (6%)
Adjusted *(b)*	2.3%	21.9%	23.1%
Terminal *(c)*	0/36 (0%)	2/14 (14%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.016	P=0.035	P=0.039
Incidental Tumor Test	P=0.129	P=0.122	P=0.246
Cochran-Armitage Trend Test	P=0.252		
Fisher Exact Test		P=0.181	P=0.309
Hematopoietic System: Monocytic Leukemia			
Tumor Rates			
Overall *(a)*	11/50 (22%)	4/50 (8%)	4/50 (8%)
Adjusted *(b)*	25.5%	19.0%	19.2%
Terminal *(c)*	5/36 (14%)	0/14 (0%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.559N	P=0.423N	P=0.574
Incidental Tumor Test	P=0.027N	P=0.053N	P=0.039N
Cochran-Armitage Trend Test	P=0.025N		
Fisher Exact Test		P=0.045N	P=0.045N

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	30 mg/kg	60 mg/kg
Liver: Neoplastic Nodule			
Tumor Rates			
Overall *(a)*	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted *(b)*	17.9%	12.0%	12.3%
Terminal *(c)*	5/36 (14%)	1/14 (7%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.520N	P=0.442N	P=0.656
Incidental Tumor Test	P=0.223N	P=0.249N	P=0.329N
Cochran-Armitage Trend Test	P=0.042N		
Fisher Exact Test		P=0.080N	P=0.080N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	3/50 (6%)	4/50 (8%)
Adjusted *(b)*	17.9%	18.8%	30.9%
Terminal *(c)*	5/36 (14%)	2/14 (14%)	1/8 (13%)
Statistical Tests *(d)*			
Life Table	P=0.177	P=0.634	P=0.199
Incidental Tumor Test	P=0.469	P=0.450N	P=0.559
Cochran-Armitage Trend Test	P=0.195N		
Fisher Exact Test		P=0.159N	P=0.262N
Pancreas: Acinar-Cell Adenoma			
Tumor Rates			
Overall *(a)*	1/47 (2%)	3/47 (6%)	7/49 (14%)
Adjusted *(b)*	2.9%	18.2%	59.2%
Terminal *(c)*	1/35 (3%)	2/14 (14%)	4/8 (50%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.075	P<0.001
Incidental Tumor Test	P<0.001	P=0.128	P=0.001
Cochran-Armitage Trend Test	P=0.020		
Fisher Exact Test		P=0.308	P=0.034
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall *(a)*	3/50 (6%)	4/44 (9%)	7/49 (14%)
Adjusted *(b)*	8.3%	18.3%	38.7%
Terminal *(c)*	3/36 (8%)	0/13 (0%)	1/8 (13%)
Statistical Tests *(d)*			
Life Table	P=0.001	P=0.134	P=0.002
Incidental Tumor Test	P=0.061	P=0.399	P=0.057
Cochran-Armitage Trend Test	P=0.112		
Fisher Exact Test		P=0.428	P=0.151
Pituitary: Chromophobe Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	4/44 (9%)	7/49 (14%)
Adjusted *(b)*	10.7%	18.3%	38.7%
Terminal *(c)*	3/36 (8%)	0/13 (0%)	1/8 (13%)
Statistical Tests *(d)*			
Life Table	P=0.004	P=0.220	P=0.004
Incidental Tumor Test	P=0.124	P=0.578	P=0.120
Cochran-Armitage Trend Test	P=0.196		
Fisher Exact Test		P=0.569	P=0.251

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	30 mg/kg	60 mg/kg
Pituitary: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	6/50 (12%)	4/44 (9%)	7/49 (14%)
Adjusted *(b)*	16.1%	18.3%	38.7%
Terminal *(c)*	5/36 (14%)	0/13 (0%)	1/8 (13%)
Statistical Tests *(d)*			
Life Table	P=0.013	P=0.371	P=0.012
Incidental Tumor Test	P=0.236	P=0.564N	P=0.199
Cochran-Armitage Trend Test	P=0.424		
Fisher Exact Test		P=0.454N	P=0.484
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	12/50 (24%)	7/49 (14%)	6/50 (12%)
Adjusted *(b)*	31.4%	39.5%	48.6%
Terminal *(c)*	10/36 (28%)	4/14 (29%)	2/8 (25%)
Statistical Tests *(d)*			
Life Table	P=0.080	P=0.305	P=0.112
Incidental Tumor Test	P=0.313	P=0.563	P=0.374
Cochran-Armitage Trend Test	P=0.071N		
Fisher Exact Test		P=0.166N	P=0.096N
Adrenal: All Pheochromocytomas			
Tumor Rates			
Overall *(a)*	12/50 (24%)	7/49 (14%)	7/50 (14%)
Adjusted *(b)*	31.4%	39.5%	57.1%
Terminal *(c)*	10/36 (28%)	4/14 (29%)	3/8 (38%)
Statistical Tests *(d)*			
Life Table	P=0.034	P=0.305	P=0.043
Incidental Tumor Test	P=0.172	P=0.563	P=0.199
Cochran-Armitage Trend Test	P=0.118N		
Fisher Exact Test		P=0.166N	P=0.154N
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	3/46 (7%)	4/49 (8%)	2/47 (4%)
Adjusted *(b)*	8.3%	23.8%	25.0%
Terminal *(c)*	3/36 (8%)	2/14 (14%)	2/8 (25%)
Statistical Tests *(d)*			
Life Table	P=0.099	P=0.110	P=0.236
Incidental Tumor Test	P=0.216	P=0.265	P=0.236
Cochran-Armitage Trend Test	P=0.405N		
Fisher Exact Test		P=0.536	P=0.490N
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/47 (2%)	0/47 (0%)	4/49 (8%)
Adjusted *(b)*	2.9%	0.0%	24.2%
Terminal *(c)*	1/35 (3%)	0/14 (0%)	1/8 (13%)
Statistical Tests *(d)*			
Life Table	P=0.007	P=0.682N	P=0.013
Incidental Tumor Test	P=0.075	P=0.682N	P=0.180
Cochran-Armitage Trend Test	P=0.088		
Fisher Exact Test		P=0.500N	P=0.194

TABLE F1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Control	30 mg/kg	60 mg/kg
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	19.4%	7.1%	20.1%
Terminal *(c)*	7/36 (19%)	1/14 (7%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.436	P=0.265N	P=0.360
Incidental Tumor Test	P=0.517N	P=0.265N	P=0.638
Cochran-Armitage Trend Test	P=0.090N		
Fisher Exact Test		P=0.030N	P=0.159N
Preputial Gland: Adenoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	0/50 (0%)	1/50 (2%)
Adjusted *(b)*	18.7%	0.0%	7.7%
Terminal *(c)*	6/36 (17%)	0/14 (0%)	0/8 (0%)
Statistical Tests *(d)*			
Life Table	P=0.174N	P=0.094N	P=0.463N
Incidental Tumor Test	P=0.103N	P=0.064N	P=0.317N
Cochran-Armitage Trend Test	P=0.007N		
Fisher Exact Test		P=0.006N	P=0.030N
Testis: Interstitial Cell Tumor			
Tumor Rates			
Overall *(a)*	48/50 (96%)	35/50 (70%)	29/50 (58%)
Adjusted *(b)*	100.0%	100.0%	96.7%
Terminal *(c)*	36/36 (100%)	14/14 (100%)	7/8 (88%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P=0.339N	P=0.520	P=0.515N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P<0.001N	P<0.001N
Testis: Interstitial Cell Tumor or Interstitial Cell Tumor, Malignant			
Tumor Rates			
Overall *(a)*	48/50 (96%)	35/50 (70%)	30/50 (60%)
Adjusted *(b)*	100.0%	100.0%	96.7%
Terminal *(c)*	36/36 (100%)	14/14 (100%)	7/8 (88%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P=0.539N	P=0.520	P=0.602
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P<0.001N	P<0.001N

(a) Number of tumor-bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study 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 lower incidence is indicated by (N).

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Control	60 mg/kg	120 mg/kg
Subcutaneous Tissue: Fibroma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted *(b)*	0.0%	5.3%	35.7%
Terminal *(c)*	0/36 (0%)	1/19 (5%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.373	P=0.001
Incidental Tumor Test	P=0.019	P=0.373	P=0.083
Cochran-Armitage Trend Test	P=0.060		
Fisher Exact Test		P=0.500	P=0.121
Subcutaneous Tissue: Fibroadenoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted *(b)*	4.9%	18.1%	16.1%
Terminal *(c)*	1/36 (3%)	1/19 (5%)	0/6 (0%)
Statistical Tests *(d)*			
Life Table	P=0.085	P=0.130	P=0.266
Incidental Tumor Test	P=0.496N	P=0.341	P=0.625N
Cochran-Armitage Trend Test	P=0.588		
Fisher Exact Test		P=0.339	P=0.691
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted *(b)*	5.3%	5.3%	51.8%
Terminal *(c)*	1/36 (3%)	1/19 (5%)	2/6 (33%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.715N	P<0.001
Incidental Tumor Test	P=0.038	P=0.609N	P=0.092
Cochran-Armitage Trend Test	P=0.133		
Fisher Exact Test		P=0.500N	P=0.218
Hematopoietic System: Monocytic Leukemia			
Tumor Rates			
Overall *(a)*	21/50 (42%)	7/50 (14%)	4/50 (8%)
Adjusted *(b)*	47.4%	26.3%	32.9%
Terminal *(c)*	13/36 (36%)	2/19 (11%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.168N	P=0.120N	P=0.392N
Incidental Tumor Test	P<0.001N	P=0.006N	P=0.001N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.002N	P<0.001N
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	22/50 (44%)	7/50 (14%)	4/50 (8%)
Adjusted *(b)*	48.7%	26.3%	32.9%
Terminal *(c)*	13/36 (36%)	2/19 (11%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.133N	P=0.096N	P=0.345N
Incidental Tumor Test	P<0.001N	P=0.002N	P<0.001N
Cochran-Armitage Trend Test	P<0.001N		
Fisher Exact Test		P=0.001N	P<0.001N

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Control	60 mg/kg	120 mg/kg
Liver: Neoplastic Nodule			
Tumor Rates			
Overall *(a)*	3/50 (6%)	8/50 (16%)	8/48 (17%)
Adjusted *(b)*	8.0%	30.6%	60.1%
Terminal *(c)*	2/36 (6%)	3/19 (16%)	3/6 (50%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.014	P<0.001
Incidental Tumor Test	P=0.035	P=0.068	P=0.022
Cochran-Armitage Trend Test	P=0.075		
Fisher Exact Test		P=0.100	P=0.087
Pituitary: Chromophobe Adenoma			
Tumor Rates			
Overall *(a)*	25/50 (50%)	15/49 (31%)	16/49 (33%)
Adjusted *(b)*	60.6%	55.5%	79.2%
Terminal *(c)*	20/36 (56%)	8/19 (42%)	3/6 (50%)
Statistical Tests *(d)*			
Life Table	P=0.003	P=0.487	P<0.001
Incidental Tumor Test	P=0.497N	P=0.336N	P=0.560
Cochran-Armitage Trend Test	P=0.046N		
Fisher Exact Test		P=0.039N	P=0.061N
Pituitary: Chromophobe Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	27/50 (54%)	15/49 (31%)	16/49 (33%)
Adjusted *(b)*	63.9%	55.5%	79.2%
Terminal *(c)*	21/36 (58%)	8/19 (42%)	3/6 (50%)
Statistical Tests *(d)*			
Life Table	P=0.007	P=0.549N	P=0.003
Incidental Tumor Test	P=0.319N	P=0.201N	P=0.463N
Cochran-Armitage Trend Test	P=0.019		
Fisher Exact Test		P=0.015N	P=0.026N
Adrenal: Cortical Adenoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	3/50 (6%)	5/48 (10%)
Adjusted *(b)*	5.6%	12.1%	46.5%
Terminal *(c)*	2/36 (6%)	1/19 (5%)	2/6 (33%)
Statistical Tests *(d)*			
Life Table	P=0.003	P=0.263	P=0.002
Incidental Tumor Test	P=0.064	P=0.395	P=0.043
Cochran-Armitage Trend Test	P=0.144		
Fisher Exact Test		P=0.500	P=0.201
Adrenal: Pheochromocytoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	5/50 (10%)	4/48 (8%)
Adjusted *(b)*	5.3%	22.2%	43.2%
Terminal *(c)*	1/36 (3%)	3/19 (16%)	2/6 (33%)
Statistical Tests *(d)*			
Life Table	P=0.003	P=0.055	P=0.004
Incidental Tumor Test	P=0.074	P=0.130	P=0.137
Cochran-Armitage Trend Test	P=0.263		
Fisher Exact Test		P=0.218	P=0.319

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Control	60 mg/kg	120 mg/kg
Thyroid: C-Cell Adenoma			
Tumor Rates			
Overall *(a)*	7/50 (14%)	0/47 (0%)	2/41 (5%)
Adjusted *(b)*	18.4%	0.0%	25.0%
Terminal *(c)*	6/36 (17%)	0/19 (0%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.393N	P=0.050N	P=0.546
Incidental Tumor Test	P=0.221N	P=0.040N	P=0.555N
Cochran-Armitage Trend Test	P=0.048N		
Fisher Exact Test		P=0.008N	P=0.136N
Thyroid: C-Cell Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/47 (9%)	1/41 (2%)
Adjusted *(b)*	2.8%	17.9%	2.9%
Terminal *(c)*	1/36 (3%)	3/19 (16%)	0/6 (0%)
Statistical Tests *(d)*			
Life Table	P=0.172	P=0.055	P=0.538
Incidental Tumor Test	P=0.318	P=0.062	P=0.734
Cochran-Armitage Trend Test	P=0.522		
Fisher Exact Test		P=0.162	P=0.701
Thyroid: C-Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	8/50 (16%)	4/47 (9%)	3/41 (7%)
Adjusted *(b)*	21.1%	17.9%	27.2%
Terminal *(c)*	7/36 (19%)	3/19 (16%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.406	P=0.545N	P=0.396
Incidental Tumor Test	P=0.462N	P=0.497N	P=0.597N
Cochran-Armitage Trend Test	P=0.117N		
Fisher Exact Test		P=0.210N	P=0.174N
Pancreatic Islets: Islet Cell Adenoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	6/49 (12%)	2/47 (4%)
Adjusted *(b)*	0.0%	24.2%	33.3%
Terminal *(c)*	0/36 (0%)	3/19 (16%)	2/6 (33%)
Statistical Tests *(d)*			
Life Table	P=0.008	P=0.003	P=0.006
Incidental Tumor Test	P=0.054	P=0.010	P=0.006
Cochran-Armitage Trend Test	P=0.229		
Fisher Exact Test		P=0.012	P=0.232
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	7/49 (14%)	2/47 (4%)
Adjusted *(b)*	0.0%	29.0%	33.3%
Terminal *(c)*	0/36 (0%)	4/19 (21%)	2/6 (33%)
Statistical Tests *(d)*			
Life Table	P=0.005	P<0.001	P=0.006
Incidental Tumor Test	P=0.038	P=0.004	P=0.006
Cochran-Armitage Trend Test	P=0.238		
Fisher Exact Test		P=0.006	P=0.232

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Control	60 mg/kg	120 mg/kg
Mammary Gland: Fibroadenoma			
Tumor Rates			
Overall *(a)*	15/50 (30%)	21/50 (42%)	18/50 (36%)
Adjusted *(b)*	39.2%	82.8%	88.6%
Terminal *(c)*	13/36 (36%)	15/19 (79%)	4/6 (67%)
Statistical Tests *(d)*			
Life Table	P<0.001	P<0.001	P<0.001
Incidental Tumor Test	P<0.001	P=0.002	P=0.010
Cochran-Armitage Trend Test	P=0.301		
Fisher Exact Test		P=0.149	P=0.335
Clitoral Gland: Adenoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted *(b)*	0.0%	18.8%	0.0%
Terminal *(c)*	0/36 (0%)	3/19 (16%)	0/6 (0%)
Statistical Tests *(d)*			
Life Table	P=0.173	P=0.015	*(e)*
Incidental Tumor Test	P=0.295	P=0.023	*(e)*
Cochran-Armitage Trend Test	P=0.622		
Fisher Exact Test		P=0.059	*(e)*
Clitoral Gland: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted *(b)*	2.6%	18.8%	0.0%
Terminal *(c)*	0/36 (0%)	3/19 (16%)	0/6 (0%)
Statistical Tests *(d)*			
Life Table	P=0.303	P=0.053	P=0.855N
Incidental Tumor Test	P=0.619	P=0.108	P=0.362N
Cochran-Armitage Trend Test	P=0.390N		
Fisher Exact Test		P=0.181	P=0.500N
Uterus: Endometrial Stromal Polyp			
Tumor Rates			
Overall *(a)*	12/50 (24%)	9/50 (18%)	8/47 (17%)
Adjusted *(b)*	30.1%	33.2%	35.3%
Terminal *(c)*	9/36 (25%)	4/19 (21%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.084	P=0.366	P=0.096
Incidental Tumor Test	P=0.374N	P=0.563N	P=0.491N
Cochran-Armitage Trend Test	P=0.229N		
Fisher Exact Test		P=0.312N	P=0.276N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Tumor Rates			
Overall *(a)*	13/50 (26%)	9/50 (18%)	8/47 (17%)
Adjusted *(b)*	31.7%	33.2%	35.3%
Terminal *(c)*	9/36 (25%)	4/19 (21%)	1/6 (17%)
Statistical Tests *(d)*			
Life Table	P=0.127	P=0.445	P=0.144
Incidental Tumor Test	P=0.241N	P=0.443N	P=0.317N
Cochran-Armitage Trend Test	P=0.164N		
Fisher Exact Test		P=0.235N	P=0.205N

TABLE F2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence in surviving animals killed at end of study.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying before the end of the study 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 lower incidence is indicated by (N).
(e) Not significant. No tumors observed in dosed and control groups.

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Control	120 mg/kg	240 mg/kg
Skin: Fibrosarcoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	4/49 (8%)	0/50 (0%)
Adjusted *(b)*	0.0%	9.4%	0.0%
Terminal *(c)*	0/46 (0%)	2/40 (5%)	0/26 (0%)
Statistical Tests *(d)*			
Life Table	P=0.469	P=0.052	*(e)*
Incidental Tumor Test	P=0.573N	P=0.066	*(e)*
Cochran-Armitage Trend Test	P=0.621		
Fisher Exact Test		P=0.056	*(e)*
Skin or Subcutaneous Tissue: Fibrosarcoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	4/49 (8%)	0/50 (0%)
Adjusted *(b)*	2.0%	9.4%	0.0%
Terminal *(c)*	0/46 (0%)	2/40 (5%)	0/26 (0%)
Statistical Tests *(d)*			
Life Table	P=0.559N	P=0.150	P=0.585N
Incidental Tumor Test	P=0.276N	P=0.194	P=0.331N
Cochran-Armitage Trend Test	P=0.391N		
Fisher Exact Test		P=0.175	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma			
Tumor Rates			
Overall *(a)*	1/50 (2%)	3/48 (6%)	2/49 (4%)
Adjusted *(b)*	2.2%	7.7%	7.7%
Terminal *(c)*	1/46 (2%)	3/39 (8%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.200	P=0.249	P=0.306
Incidental Tumor Test	P=0.200	P=0.249	P=0.306
Cochran-Armitage Trend Test	P=0.392		
Fisher Exact Test		P=0.293	P=0.492
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	5/48 (10%)	2/49 (4%)
Adjusted *(b)*	4.3%	12.3%	7.7%
Terminal *(c)*	2/46 (4%)	4/39 (10%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.321	P=0.161	P=0.476
Incidental Tumor Test	P=0.387	P=0.180	P=0.476
Cochran-Armitage Trend Test	P=0.573		
Fisher Exact Test		P=0.201	P=0.684
Hematopoietic System: Malignant Lymphoma			
Tumor Rates			
Overall *(a)*	6/50 (12%)	5/49 (10%)	3/50 (6%)
Adjusted *(b)*	13.0%	12.5%	10.9%
Terminal *(c)*	6/46 (13%)	5/40 (13%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.496N	P=0.598N	P=0.565N
Incidental Tumor Test	P=0.434N	P=0.598N	P=0.474N
Cochran-Armitage Trend Test	P=0.196N		
Fisher Exact Test		P=0.514N	P=0.243N

TABLE F3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Control	120 mg/kg	240 mg/kg
Liver: Adenoma			
Tumor Rates			
Overall *(a)*	5/49 (10%)	3/48 (6%)	2/50 (4%)
Adjusted *(b)*	10.9%	7.5%	7.7%
Terminal *(c)*	5/46 (11%)	3/40 (7%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.382N	P=0.435N	P=0.491N
Incidental Tumor Test	P=0.382N	P=0.435N	P=0.491N
Cochran-Armitage Trend Test	P=0.153N		
Fisher Exact Test		P=0.369N	P=0.210N
Liver: Carcinoma			
Tumor Rates			
Overall *(a)*	6/49 (12%)	9/48 (19%)	3/50 (6%)
Adjusted *(b)*	13.0%	20.7%	9.8%
Terminal *(c)*	6/46 (13%)	6/40 (15%)	0/26 (0%)
Statistical Tests *(d)*			
Life Table	P=0.552N	P=0.207	P=0.546N
Incidental Tumor Test	P=0.144N	P=0.321	P=0.233N
Cochran-Armitage Trend Test	P=0.211N		
Fisher Exact Test		P=0.273	P=0.233N
Liver: Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	11/49 (22%)	12/48 (25%)	5/50 (10%)
Adjusted *(b)*	23.9%	27.7%	16.7%
Terminal *(c)*	11/46 (24%)	9/40 (23%)	2/26 (8%)
Statistical Tests *(d)*			
Life Table	P=0.418N	P=0.359	P=0.420N
Incidental Tumor Test	P=0.114N	P=0.481	P=0.193N
Cochran-Armitage Trend Test	P=0.073N		
Fisher Exact Test		P=0.477	P=0.079N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values 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 non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(e) Not significant. No tumors observed in dosed and control groups.

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Control	60 mg/kg	120 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted *(b)*	0.0%	7.0%	3.0%
Terminal *(c)*	0/33 (0%)	3/43 (7%)	1/33 (3%)
Statistical Tests *(d)*			
Life Table	P=0.372	P=0.172	P=0.500
Incidental Tumor Test	P=0.372	P=0.172	P=0.500
Cochran-Armitage Trend Test	P=0.384		
Fisher Exact Test		P=0.125	P=0.505
Hematopoietic System: Leukemia			
Tumor Rates			
Overall *(a)*	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted *(b)*	7.4%	0.0%	0.0%
Terminal *(c)*	0/34 (0%)	0/43 (0%)	0/33 (0%)
Statistical Tests *(d)*			
Life Table	P=0.040N	P=0.102N	P=0.147N
Incidental Tumor Test	P=0.119N	P=0.414N	P=0.240N
Cochran-Armitage Trend Test	P=0.037N		
Fisher Exact Test		P=0.121N	P=0.121N
Hematopoietic System: Malignant Lymphoma			
Tumor Rates			
Overall *(a)*	10/50 (20%)	17/50 (34%)	16/50 (32%)
Adjusted *(b)*	25.8%	38.6%	44.2%
Terminal *(c)*	7/34 (21%)	16/43 (37%)	13/33 (39%)
Statistical Tests *(d)*			
Life Table	P=0.082	P=0.241	P=0.101
Incidental Tumor Test	P=0.029	P=0.085	P=0.033
Cochran-Armitage Trend Test	P=0.112		
Fisher Exact Test		P=0.088	P=0.127
Hematopoietic System: Lymphoma or Leukemia			
Tumor Rates			
Overall *(a)*	13/50 (26%)	17/50 (34%)	16/50 (32%)
Adjusted *(b)*	31.3%	38.6%	44.2%
Terminal *(c)*	7/34 (21%)	16/43 (37%)	13/33 (39%)
Statistical Tests *(d)*			
Life Table	P=0.241	P=0.503	P=0.273
Incidental Tumor Test	P=0.089	P=0.151	P=0.098
Cochran-Armitage Trend Test	P=0.294		
Fisher Exact Test		P=0.257	P=0.330
Circulatory System: Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted *(b)*	0.0%	0.0%	8.0%
Terminal *(c)*	0/34 (0%)	0/43 (0%)	0/33 (0%)
Statistical Tests *(d)*			
Life Table	P=0.029	*(e)*	P=0.105
Incidental Tumor Test	P=0.015	*(e)*	P=0.037
Cochran-Armitage Trend Test	P=0.037		
Fisher Exact Test		*(e)*	P=0.121

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Control	60 mg/kg	120 mg/kg
Circulatory System: Hemangioma or Hemangiosarcoma			
Tumor Rates			
Overall *(a)*	0/50 (0%)	1/50 (2%)	5/50 (10%)
Adjusted *(b)*	0.0%	2.3%	13.3%
Terminal *(c)*	0/34 (0%)	1/43 (2%)	1/33 (3%)
Statistical Tests *(d)*			
Life Table	P=0.008	P=0.547	P=0.029
Incidental Tumor Test	P=0.003	P=0.547	P=0.005
Cochran-Armitage Trend Test	P=0.011		
Fisher Exact Test		P=0.500	P=0.028
Liver: Hepatocellular Adenoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	3/50 (6%)	12/50 (24%)
Adjusted *(b)*	5.3%	6.7%	36.4%
Terminal *(c)*	1/34 (3%)	2/43 (5%)	12/33 (36%)
Statistical Tests *(d)*			
Life Table	P<0.001	P=0.571	P=0.003
Incidental Tumor Test	P<0.001	P=0.325	P=0.003
Cochran-Armitage Trend Test	P=0.001		
Fisher Exact Test		P=0.500	P=0.004
Liver: Hepatocellular Carcinoma			
Tumor Rates			
Overall *(a)*	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted *(b)*	5.0%	4.7%	8.8%
Terminal *(c)*	1/34 (3%)	2/43 (5%)	2/33 (6%)
Statistical Tests *(d)*			
Life Table	P=0.376	P=0.629N	P=0.463
Incidental Tumor Test	P=0.248	P=0.644	P=0.308
Cochran-Armitage Trend Test	P=0.406		
Fisher Exact Test		P=0.691	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Tumor Rates			
Overall *(a)*	4/50 (8%)	5/50 (10%)	15/50 (30%)
Adjusted *(b)*	10.1%	11.2%	44.1%
Terminal *(c)*	2/34 (6%)	4/43 (9%)	14/33 (42%)
Statistical Tests *(d)*			
Life Table	P=0.001	P=0.601	P=0.004
Incidental Tumor Test	P<0.001	P=0.321	P=0.001
Cochran-Armitage Trend Test	P=0.002		
Fisher Exact Test		P=0.500	P=0.005
Pituitary: Adenoma			
Tumor Rates			
Overall *(a)*	4/46 (9%)	3/44 (7%)	1/43 (2%)
Adjusted *(b)*	11.3%	7.7%	3.2%
Terminal *(c)*	3/33 (9%)	3/39 (8%)	1/31 (3%)
Statistical Tests *(d)*			
Life Table	P=0.143N	P=0.417N	P=0.204N
Incidental Tumor Test	P=0.160N	P=0.500N	P=0.221N
Cochran-Armitage Trend Test	P=0.150N		
Fisher Exact Test		P=0.525N	P=0.202N

TABLE F4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Control	60 mg/kg	120 mg/kg
Skeletal System: Osteosarcoma			
Tumor Rates			
Overall *(a)*	4 50 (8%)	0 50 (0%)	1 50 (2%)
Adjusted *(b)*	9.2%	0.0%	2.8%
Terminal *(c)*	0 34 (0%)	0 43 (0%)	0 33 (0%)
Statistical Tests *(d)*			
Life Table	P=0.098N	P=0.057N	P=0.225N
Incidental Tumor Test	P=0.309N	P=0.343N	P=0.472N
Cochran-Armitage Trend Test	P=0.082N		
Fisher Exact Test		P=0.059N	P=0.181N

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

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

(c) Observed tumor incidence at terminal kill.

(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

(e) Not significant. No tumors observed in dosed and control groups.

APPENDIX G

ANALYSIS OF TOLUENE DIISOCYANATE

APPENDIX G

A. ELEMENTAL ANALYSIS

Element	C	H	N
Theory	62.07	3.47	16.09
1. Lot No. 228: Determined	62.40	3.64	16.40
	62.33	3.60	16.35
2. Lot No. 414417: Determined	62.46	3.61	16.89
	62.66	3.52	16.60

B. BOILING POINT

Determined	Literature Value
Lot No. 228: b.p. 254° to 255°C at 742.8 mm	b.p. ~240°C (Fieser and Fieser, 1968)

C. INDEX OF REFRACTION

Lot No. 228: n_D^{20} 1.5687	n_D^{25} 1.5658 for 99.6% in chlorobenzene (Goldberg et al., 1959)

D. TITRATION

1. Procedure

Reaction of the isocyanate groups with an excess of di-n-butylamine and titration of the unreacted amine with 1.0 N hydrochloric acid using bromophenol blue as an indicator (Annual Book of ASTM Standards, 1974).

2. Results

Lot. No. 414417 102.6% ± 0.7(δ)%

E. VAPOR PHASE CHROMATOGRAPHY

1. Lot No. 228

Instrument: Tracor MT-220

Column: 3% OV-1 on 80/100 Supelcoport, 1.8 m x 4 mm I.D.

Detector: Flame ionization

Oven Temperature Program: 5 min hold at 100°C, then programmed from 100° to 235°C at 10°C/min

Results: Major peak and six impurities

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Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak Area)
1	2.2	0.29	Trace
2	5.2	0.68	Trace
3	5.4	0.71	Trace
4	7.6	1.00	100
5	8.9	1.17	Trace
6	9.3	1.22	Trace
7	16.4	2.16	Trace

2. Lot No. 414417

Instrument: Hewlett-Packard 5730A

Detector: Flame ionization

Inlet Temperature: 200°C

Detector Temperature: 250°C

Carrier Gas: Nitrogen

a. System 1

Column: 3% SP-2100 on 100/120 Supelcoport, 1.8 m x 2 mm I.D., silylated glass

Carrier Flow Rate: 70 ml/min

Oven Temperature Program: Initial 4-min hold at 75°C followed by a 8°C/min increase to 250°C for the detection of impurities; isothermal at 125°C for major peak area determination.

Samples Injected: 5 μl of a 10% (v/v) solution in hexane to detect and determine the area of impurities; 3-5 μl of 1.0 and 0.5% (v/v) solutions in hexane to determine major peak area and linearity of detector response.

Results: Twelve impurities, four preceding and eight following the major peaks, were detected. Only two of the impurities had relative areas <0.1%.

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak Area)
1	13.3	1.00	100
2	15.6	1.17	0.2
3	27.3	2.05	0.2

b. System 2

Column: 3% Dexsil 400 on 80 100 Chromosorb W(AW), 1.8 m x 4 mm I.D., silylated glass

Carrier Flow Rate: 70 ml min

Oven Temperature Program: Initial hold at 70°C for 4 min, programmed to 250°C at 8°C min for impurity detection.

Isothermal at 140°C to monitor detector response.

Samples Injected: 6 µl of 10%, 1%, and 0.5% (v v) solutions in n-pentane to detect and determine relative areas of all volatile impurities.

Results: One major peak followed by two impurities with relative areas greater than 0.1% were detected.

Peak	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (Percent of Major Peak Area)
1	14.1	1.00	100.0
2	15.7	1.12	0.21
3	26.0	1.85	0.15

F. SPECTRAL DATA

1. Infrared (Both lots)

Instrument: Beckman IR 12
Cell: Neat liquid between sodium chloride plates (Lot 228) or silver chloride plates (Lot 41447)
Results: See Figures 7 and 8

The spectra were consistent with a literature spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible:

a. Lot No. 228
Instrument: Cary 118

λ max (nm)	ε x 10 ^{3}
284	1.03 ± 0.01(δ)

No maxima observed between 350 and 800 nm at a concentration of 1.5 mg/ml

Solvent: Heptane

Literature Values

λ max (nm)	ε x 10 ^{3}
282	1.3
290	(shoulder)

Solvent: Dioxane

b. Lot No. 414417

λ max (nm)	ε x 10 ^{3}
284	0.95 ± 0.01
290 (shoulder)	0.89 ± 0.01

Solvent: n-Pentane

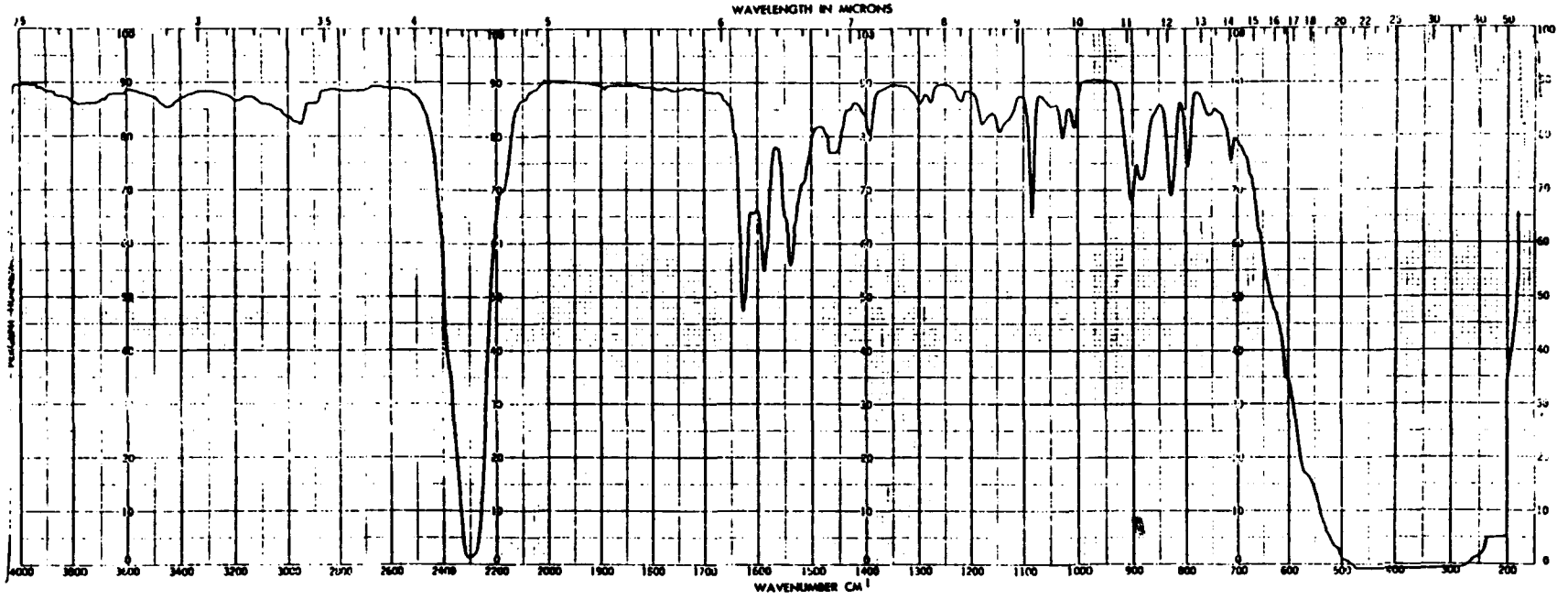

Figure 7. Infrared Absorption Spectrum of Toluene Diisocyanate (Lot No. 228)

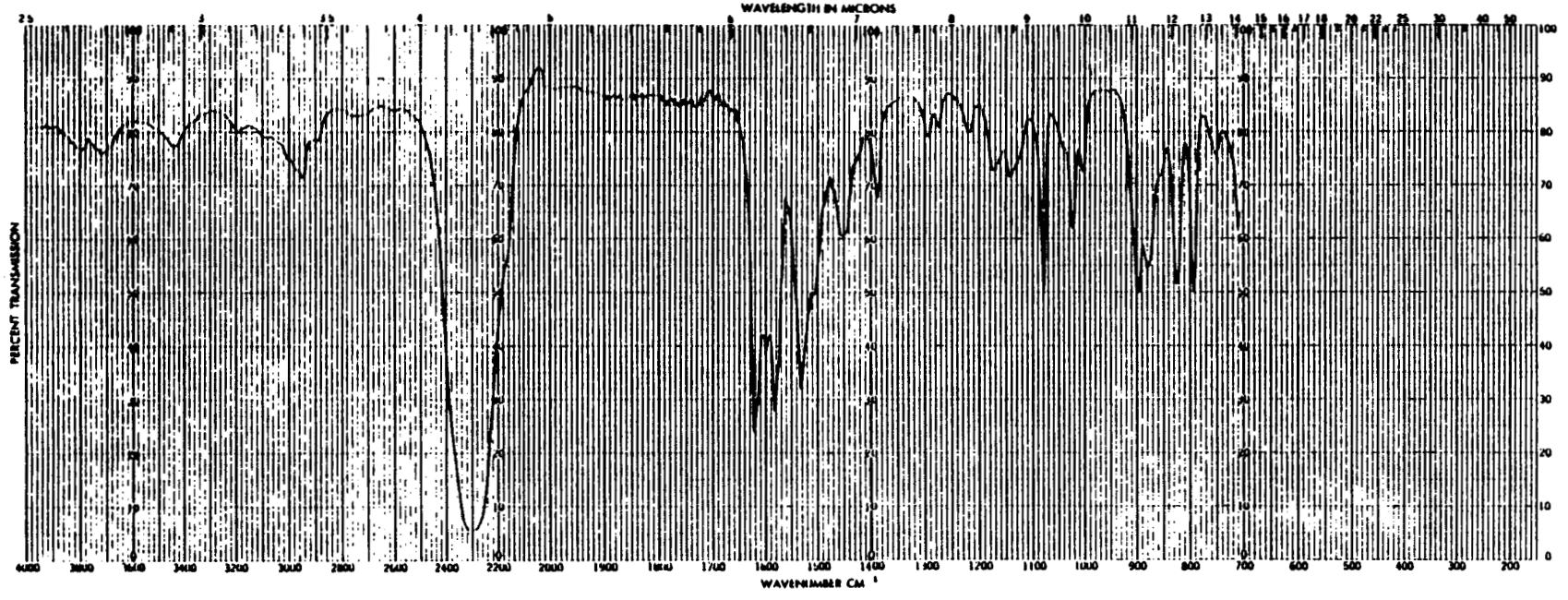

Figure 8. Infrared Absorption Spectrum of Toluene Diisocyanate (Lot No. 414417)

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G. NUCLEAR MAGNETIC RESONANCE

1. Lot No. 228

Instrument: Varian HA-100

Solvent: Neat with added internal tetramethylsilane

Assignments: See Figure 9

No literature spectrum found.

Spectrum consistent with literature spectrum for 2,4-isomer (Sadtler Standard Spectra)

79.7% 2,4-Toluene diisocyanate; 20.3% 2,6-toluene diisocyanate

(a) s, δ = 2.06 ppm
(b) d, δ = 6.39 ppm (J_{bc} = 2 Hz)
(c) d, AB pattern, δ = 6.57 ppm (J_{cd} = 8 Hz)
(d) d, δ = 6.85 ppm
(e) s, δ = 2.00 ppm
(f) d, δ = 6.65 ppm (J_{fg} = 9 Hz)
(g) t, δ = 6.85 ppm

Integration Ratios:

(a) 3.00
(b) 1.02
(c) 1.1
(d) 1.2
(e) 3.00
(f) 2.1
(g) 1.2

2. Lot No. 414417

Instrument: Varian EM360

Solvent: Neat with a TMS internal standard

Assignments: See Figure 10

Consistent with literature spectrum for 2,4-isomer and also with the spectra of the mixed isomers for Lot No. 228

Determined

(a) s, δ = 2.07 ppm
(b) d, δ = 6.42 ppm, J_{bc} = 2 Hz
(c) d, δ = 6.57 ppm, J_{cd} = 8 Hz
(d) d, δ = 6.92 ppm
(e) s, δ = 2.01 ppm
(f) d, δ = 6.69 ppm, J_{fg} = 8 Hz
(g) t, δ = 6.93 ppm

Integration Ratios:

(a), (b), (c), (f) 8.25/3.29 = 2.51
(b), (c), (f) 6.36/3.29 = 1.93
(d), (g) 3.80/3.29 = 1.15
(e) 1.41/3.79 = 0.43

Isomer Ratio:

Percent 2,4 = 8.25/9.66 x 100 = 85.4
Percent 2,6 = 1.41/9.66 x 100 = 14.6

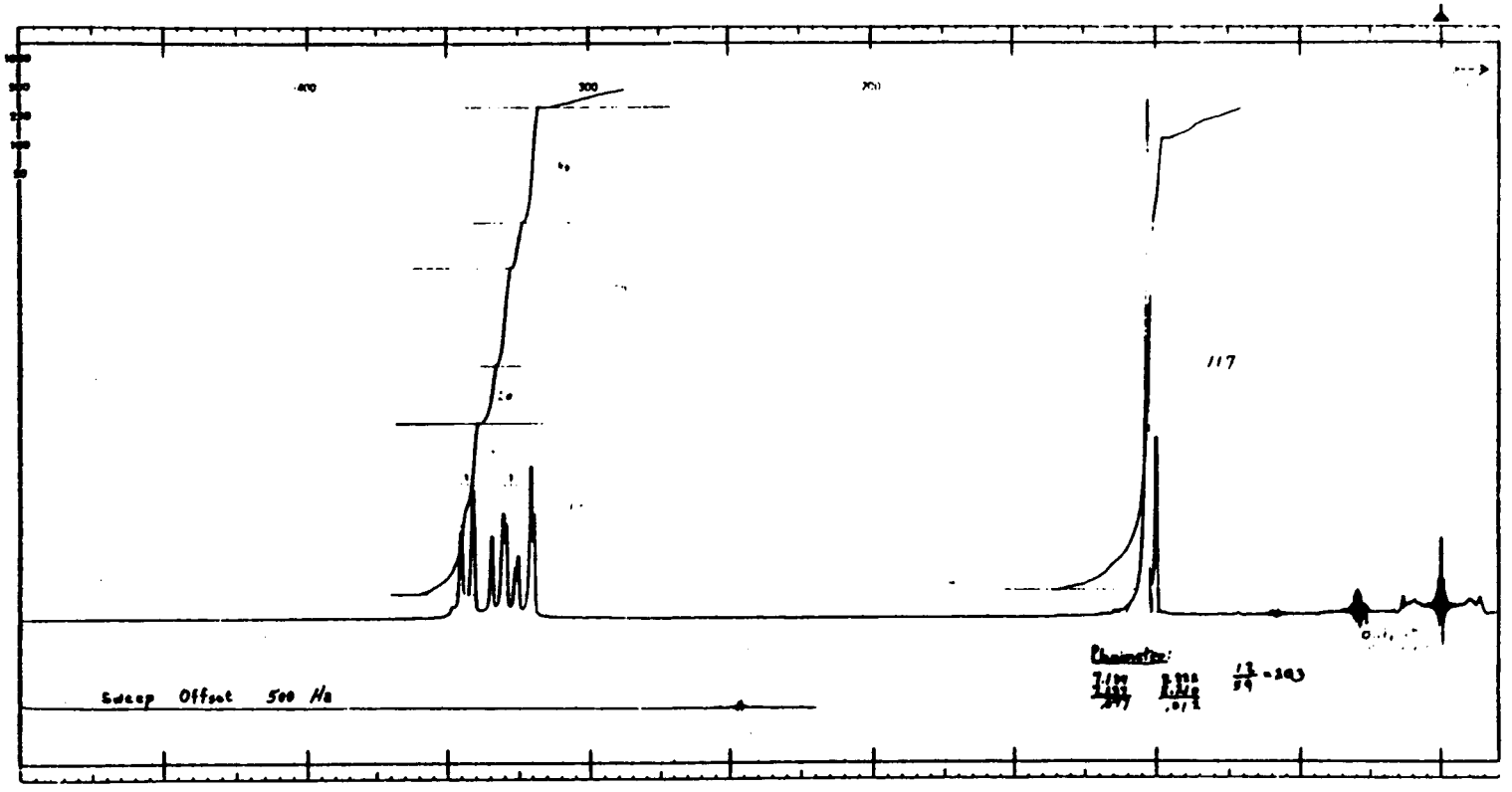

Figure 9. Nuclear Magnetic Resonance Spectrum of Toluene Diisocyanate (Lot No. 228)

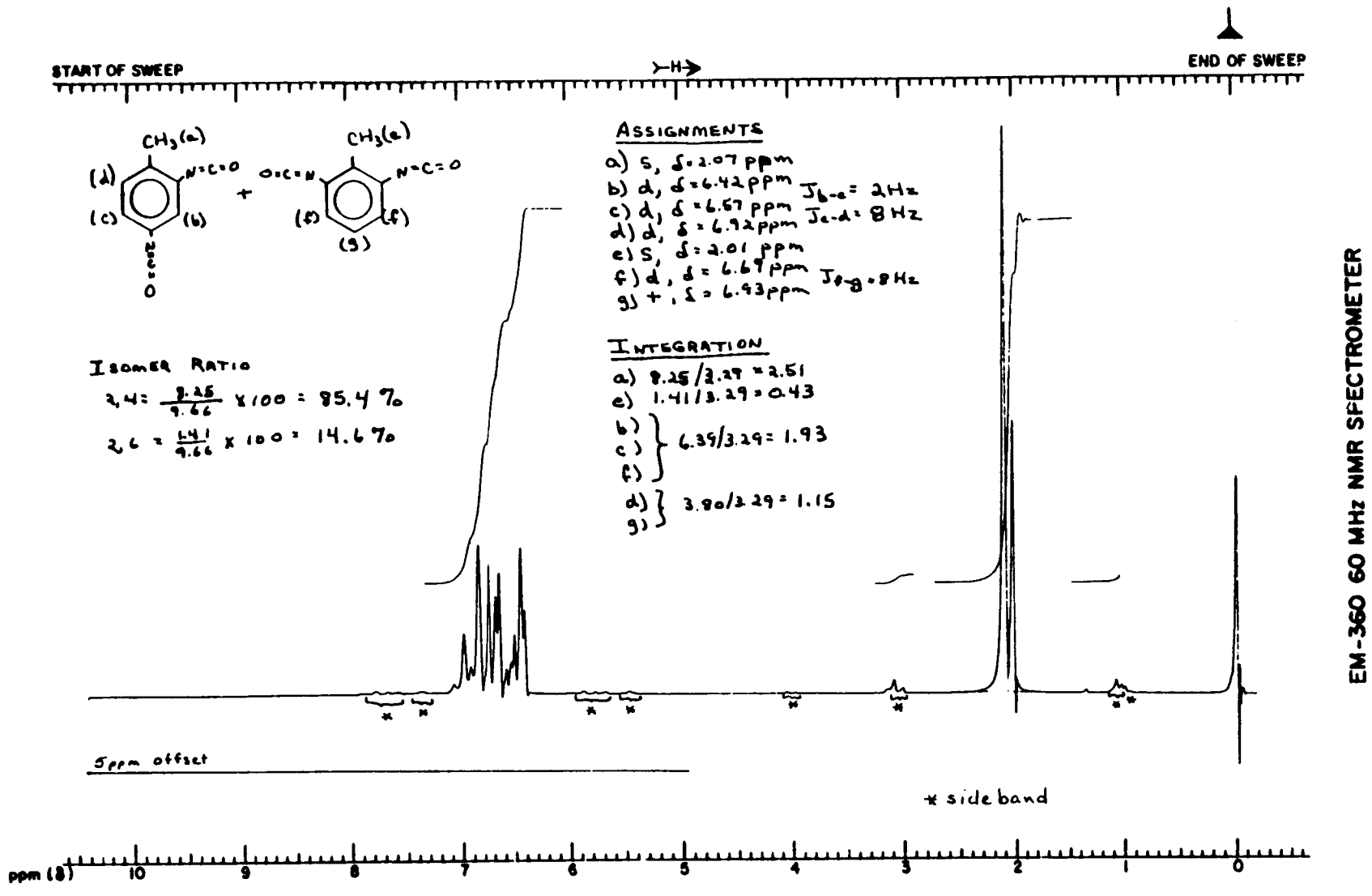

Figure 10. Nuclear Magnetic Resonance Spectrum of Toluene Diisocyanate (Lot No. 414417)

APPENDIX H

ANALYSIS OF TOLUENE DIISOCYANATE FOR DISUBSTITUTED UREAS

APPENDIX H

A. ANALYSIS

A sample of TDI stored in a septum vial and free of precipitate or suspended material was analyzed for nonvolatile residue by the following procedure.

A 50-ml round bottom flask (chromic acid washed, rinsed, and oven dried) was flame dried while being flushed with dry N_2. It was then immediately connected to a dry ice acetone trap and vacuum pump, and a vacuum was drawn until the flask had cooled. The vacuum was released through a valve fitted with a $CaSO_4$ tube. An inverted funnel was arranged directly above the flask and connected via a $CaSO_4$ drying tube to a N_2 tank. The N_2 flow rate was adjusted to provide a N_2 atmosphere in the immediate vicinity of the flask. Within the cone of the inverted funnel, the TDI vial was opened and approximately 20 g of TDI was poured into the flask. The vacuum was then reapplied and the flask heated to approximately 100°C with an electric heating mantle. Gentle hand swirling of the flask was used to prevent bumping. When only a few grams of TDI remained, the flask was cooled and the vacuum released. The contents were then transferred, under N_2 with a Pasteur pipette and two 2-ml acetonitrile washes (Burdick and Jackson, UV grade), into a dry, tared, 10-ml round bottom flask. The vacuum was reapplied and evaporation conducted as before. This was continued for 30 minutes after no liquid remained in the flask to ensure drying. The flask was then cooled, the vacuum was released, and the weight of nonvolatile residue was determined by difference on a Mettler H51AR analytical balance. This entire procedure was repeated with a second sample of TDI.

	First Determination	Second Determination
Mass of TDI	18.3 ± 0.05 g	19.9 ± 0.05 g
Mass of nonvolatile residue	0.0583 ± 0.0001 g	0.06791 ± 0.00005 g
Mass percentage	0.318 ± 0.001%	0.341 ± 0.001%

Values expressed as ± standard deviation.

The residue does not melt up to 250°C, suggesting that it is a polymer (II) (m.p. 230°C) formed from (I) (m.p. 170°-180°C) during distillation (Eight Peak Index, 1970).

B. IDENTIFICATION OF THE NONVOLATILE RESIDUE

1. Sample Preparation

a. Isolation of the Precipitate from the Sample

Ten milliliters of toluene diisocyanate containing the precipitate was centrifuged for 5 minutes, and the supernatant toluene diisocyanate was drawn off with a dispo-pipet. The precipitate was then washed with two 5-ml portions of chloroform and dried using vacuum filtration.

In addition, 4.0 ml of toluene diisocyanate, as received from Litton, was filtered through a pre-weighed 0.5 μm filter, washed with chloroform (saturated with the precipitate compound), and the isolated precipitate was dried at room temperature. The weight of precipitate per given volume of toluene diisocyanate was then calculated.

b. Preparation of Suspected Compound

Since the precipitate was suspected to be the reaction product of toluene diisocyanate with moisture in the headspace of the sample bottle, the following reactions were conducted:

(1) Reaction with Water At Elevated Temperatures

Distilled water (2 ml) was added to 2 ml of freshly filtered toluene diisocyanate in a small beaker. The mixture was swirled and gently warmed on a hotplate. When a reaction began to occur, the beaker was removed from the hotplate and allowed to cool to room temperature. The product was vacuum filtered and then spread thinly on a glass plate to dry.

(2) Reaction with Water at Room Temperature

Distilled water (2 ml) was added to 2 ml of freshly filtered toluene diisocyanate in a test tube. After 2 hours, the reaction product was isolated by vacuum filtration and then spread thinly on a glass plate to dry.

(3) Reaction with Moist Air at Room Temperature

Five milliliters of toluene diisocyanate was placed in a small uncovered beaker in a hood. After 2 days, the toluene diisocyanate had completely reacted. The product was spread thinly on a glass plate to dry.

2. Mass Spectrometry

Electron impact mass spectra (70 ev) were obtained for each of the precipitate samples using a Varian CH4-B mass spectrometer. Samples were introduced by direct inlet at a probe temperature of 220°C. The data were processed by a Varian 620/i computer.

C. RESULTS

The spectra obtained from the precipitate in the Litton sample (Figure 11) and samples reacted with water and air (Figure 12) were all consistent with a literature spectrum and with the structure of N,N'-bis-(3-isocyanato, 4-methylphenyl) urea. This compound is one of the expected reaction products of toluene diisocyanate and water. (The others should be positional isomers and possible polymers.)

Filtration of 4 ml of toluene diisocyanate (as received from Litton) yielded 21.49 mg of precipitate assumed to be bis-(3-isocyanato, 4-methyl-phenyl) urea.

Spectrum Obtained from Precipitate in Litton Sample (Figure 11)		Spectrum Obtained from the Reaction Product of Toluene Diisocyanate and Water (Figure 12)	
m/e	Relative Intensity (Percent of Base Peak)	m/e	Relative Intensity (Percent of Base Peak)
148	100	148	100
174	91	174	93
147	47	322	37
322	42	147	33
44	36	145	22
145	25	173	18
173	21	146	18
146	18	44	16
119	13	132	11
120	12	119	10
132	11	175	9
77	10	323	9
149	9	51	9
51	9	77	9
175	9	149	8
323	9		

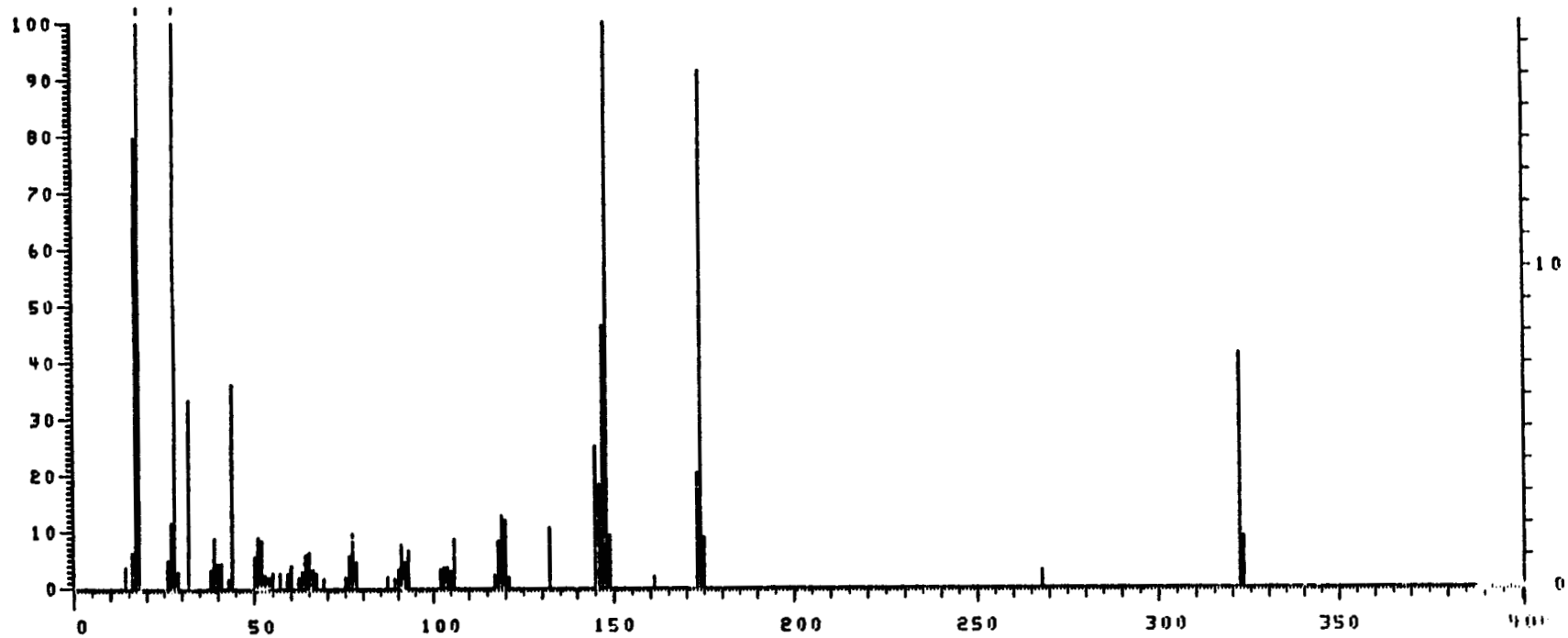

Figure 11. Mass Spectrum of Precipitate from Litton Bionetics, Inc. Sample of Toluene Diisocyanate

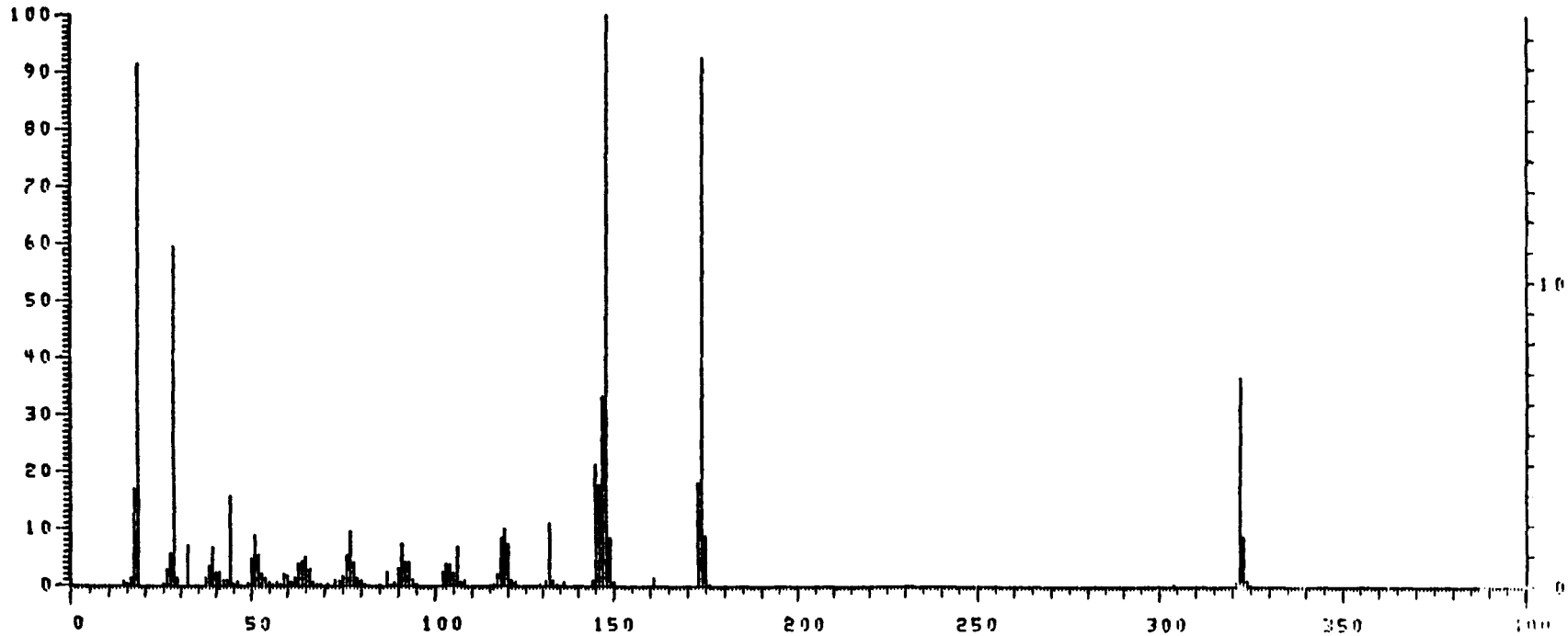

Figure 12. Mass Spectrum of Precipitate from Reaction of Toluene Diisocyanate with Water

APPENDIX H

Literature Spectrum of N,N'-Bis-(3-isocyanato, 4-methylphenyl) Urea (Eight Peak Index, 1970)

m/e	Relative Intensity (Percent of Base Peak)
148	100
174	39
147	21
146	11
44	10
149	9
43	9
57	8
M^+ 322	7.30

Isotopic contributions to the $M^+ + 1$ ion are in agreement with the molecular formula for the assigned structure.

m/e	Precipitate	Relative Intensities (Percent of m/e 322) Reaction Product with Water	Theoretical for $C_{17}H_{14}N_4O_3$
M^+ 322	100	100	100
M^++1 323	21.7	24.2	20.8

D. CONCLUSIONS

The mass spectrum of the precipitate in the Litton sample is consistent with the structure and with a literature spectrum of N,N'-bis-(3-isocyanato, 4-methylphenyl) urea. The spectrum is also identical with a spectrum obtained from the reaction product of toluene diisocyanate and water, as well as with a spectrum of the material obtained when toluene diisocyanate is allowed to react completely with moist air. Although the spectrum matches well, it is possible that the precipitate contains other positional isomers as well as polymers. The spectrum obtained probably represents the most volatile materials present. Quantitation by filtration and gravimetric analysis indicated the toluene diisocyanate from Litton contained 0.54% (w/v) or 0.44% (w/w) precipitate. Assuming the precipitate is bis-(3-isocyanato, 4-methylphenyl) urea, this represents reaction of 0.47% of the toluene diisocyanate with water.

APPENDIX I

STABILITY OF TOLUENE DIISOCYANATE IN CORN OIL

APPENDIX I

A. PURPOSE

This study was conducted to determine the stability of toluene diisocyanate at low, medium, and high dose concentrations in corn oil with a normal water content, and in corn oil which had been dried to remove as much water as possible. Also requested with the stability study was a determination of the rate of moisture absorption by the dried oil during exposure to environmental conditions similar to those encountered at the bioassayer's laboratory.

B. CORN OIL DRYING STUDIES

1. Drying Procedure

A 1-liter round bottom flask (24/40 neck) containing approximately 400 ml of corn oil was connected to a Buchi rotatory vacuum evaporator apparatus equipped with a 100°C oil bath. A vacuum of approximately 16 mm Hg was maintained over a 3-hour period while rotating the flask partially immersed in the oil bath.

At the end of the drying period, dry nitrogen was bled into the flask until atmospheric pressure had been reached; then the flask was removed from the apparatus and tightly stoppered. The residual water content of the oil was determined by the Karl Fischer analysis method below.

2. Karl Fischer Analysis Method for Water Content

a. Titrating Medium - 200 ml of reagent grade chloroform was mixed with 100 ml of anhydrous reagent grade methanol.

b. Karl Fischer Reagent - Purchased reagent approximately 5 to 7 mg/ml water titer. (Fisher Scientific Company, Catalog No. SO-K-3)

c. Diluted Karl Fischer Reagent - Reagent (B-2) diluted to a water titer of approximately 1 mg/ml using Fisher Scientific Company KF Diluent, Catalog No. SO-K-5.

d. Instrumentation and Operating Parameters

Instrument: E-536 Metrohm Herisau Potentiograph with E-456
Polarizer, E-535 Dosimat and E-549 Titrating Stand

Potentiograph Settings:
Stop-% full scale: 70%
Titrating speed: 5 min 100% vol
Range: 1 V
Counter-voltage: 300 mv
Slope adaption: 100%
Selector switch: mv pH
Volume axis: 200 mm 100% vol

Polarizer Settings:
Amps 250 mV: 100
U Pol. +: 250 mV

e. Procedure

A 50-ml volume of chloroform-methanol titrating medium was transferred to an autotitrator reaction vessel containing a magnetic stirring bar. Karl Fischer reagent (2 to 3 ml of undiluted reagent) was added and the vessel was immediately connected to the apparatus. The mixture was stirred for about 2 minutes while the headspace of the vessel was being continuously purged with a gentle stream of dry nitrogen; then the solvent mixture was automatically titrated to a zero water endpoint, using the diluted Karl Fischer reagent.

Without delay, 10 ml of corn oil sample was drawn into a dry 25-ml syringe and weighed to the nearest 0.01 g. The sample was immediately injected into the titration vessel containing the anhydrous base and was titrated to the typical zero water endpoint. The syringe was reweighed to determine the weight of the sample by difference.

f. Standardization of the Karl Fischer Reagent

The Karl Fischer titrant was standardized by adding 2, 3, and 4 μl volumes of water into 50 ml anhydrous titrating medium as prepared above, using a calibrated 10 μl syringe. The syringe was calibrated by injecting 2, 3, and 4 μl quantities of water into a small, tared septum vial and reweighing the vial. The mean weight of water from at least 3 injections of each volume was used for calculating the KF titer.

A special study was also conducted to determine whether the presence of 10 ml of corn oil in the titrating medium would have an effect on the water titer determination. For this work, 50 ml of titrating medium, 10 ml of corn oil, and 3 ml of undiluted KF were combined and titrated to anhydrous condition. Aliquots of 2, 3, and 4 μl of water were added and titrated. The results showed no significant difference from the titer values obtained with no corn oil present.

g. Calculations

The titer of the Karl Fischer reagent was computed as follows:

$$\text{KF Titer (as mg } H_2O/\text{ml)} = \frac{\mu\text{l } H_2O \text{ injected x mg } H_2O/\mu\text{l}}{\text{ml of Karl Fischer reagent used}}$$

Then using the KF titer, the water content of the samples was computed as,

$$\text{Percent } H_2O = \frac{\text{KF Titer(as mg } H_2O/\text{ml) x ml KF consumed by sample}}{\text{Sample Weight (g) x 1000}} \times 100$$

3. Experimental Summary

The experiments to find an effective method for removing water from corn oil as completely as possible were conducted under conditions which were thought to be sufficiently mild so as not to adversely affect the corn oil. The drying techniques evaluated included heating the corn oil in a rotatory vacuum evaporator for various times and temperatures and direct heating of the oil up to 135°C for varying periods of time while continuously gassing with dry nitrogen. Temperatures above 135°C were not used because of the risk of causing chemical changes in the unsaturated fatty acids in the triglycerides.

4. Results/Conclusion

It was determined from these experiments that corn oil could not be easily dried below a moisture content of approximately 0.005%. For practical reasons, drying conditions were chosen to require 3 hours of drying at 100°C on a rotatory vacuum evaporator operated at a pressure of approximately 16 mm Hg. Water analyses on different corn oils dried by this method ranged from 0.0053% to 0.0068%.

C. STABILITY OF TOLUENE DIISOCYANATE IN NORMAL AND DRY CORN OIL

1. Test Parameters

Concentrations: 9, 36, and 72 mg/ml
Vehicle: Corn oil, normal water content, and dried oil
Duration: 7 days, with sampling for analysis after 0, 1, and 7 days storage
Temperature: Room temperature

APPENDIX I

In preparing for the stability study, a decision had to be made as to what moisture content should be chosen for the "normal corn oil." Water analyses on corn oil samples from various sources ranged widely. For example, two freshly opened bottles of Mazola® corn oil purchased from a local grocery analyzed 0.029% and 0.034% water. Corn oil from a gallon bottle in current use for gavage experiments in this laboratory contained 0.045% water, and two samples of corn oil received recently from a bioassayer analyzed 0.060% and 0.69%. As a practical compromise, and for the purpose of testing the stability of TDI in two media with significantly different water contents, the "normal corn oil" used in the study was adjusted to a water content of 0.050%. The dried corn oil used for the stability study contained approximately 0.0053% water.

2. Sample Preparation and Storage

For the stability study, approximately 400 ml quantities each of normal corn oil and dried corn oil (B-1) were prepared. The oils were carefully analyzed for their water content by the Karl Fischer method (B-3); then solutions with TDI (50 ml) were prepared in duplicate at dose levels of 9, 36, and 72 mg/ml, using the normal and dried oils. The oil solutions were stored in amber glassware at room temperature for the stability study.

Analyses for TDI content were run initially and again after 1 day and 7 days of storage, using the analysis method described below.

3. Analysis Procedure for TDI

Samples (1 g) were placed into dry 50-ml amber volumetric flasks and weighed to the nearest 0.1 mg. They were then immediately prepared for gas chromatographic analysis by one of the methods described below, depending on the dose concentration.

9 mg/ml dose level - 5 ml of internal standard solution (hexadecane, 0.5 mg/ml in hexane) was added to the flask; then the contents were diluted to 50 ml with hexane and thoroughly mixed. The resulting solution was used without further dilution.

36 mg/ml dose level - The sample was diluted to 50 ml with hexane and thoroughly mixed; then, a 10-ml aliquot was pipetted into a 50-ml septum vial containing 26 ml of hexane and 4 ml of internal standard solution (see 9 mg/ml dose). After sealing and mixing thoroughly, the TDI content of the solution was determined by the gas chromatography system described below.

Vial seals were Microsep F-138 gas chromatography septa with Teflon® film facing available from Canton Biomedical Products, Inc., Boulder, Colorado 80302; the aluminum crimp seals and vials are available from Wheaton Scientific Company, Inc., Millville, New Jersey.

72 mg/ml dose level - The sample was diluted to 50 ml with hexane and thoroughly mixed; then, a 5-ml aliquot was pipetted into a 50-ml septum vial containing 31 ml of hexane and 4 ml of internal standard solution (see 9 mg/ml dose). After sealing and mixing thoroughly, the TDI content of the solution was determined by the gas chromatography system described below.

Instrument: Varian 3700 gas chromatograph with a CDS-111 Integrator and Autosampler

Column: 3% OV-17 on 100/120 mesh Supelcoport, 1.8 m x 2 mm I.D., glass, silanized

Detector: Flame Ionization

Temperatures: Oven, 130°C isothermal
Injector, 160°C
Detector, 250°C

Carrier Gas: Nitrogen

Volume Injected: 3 μl

Retention Times: TDI - 2.6 min
Hexadecane - 4.1 min

APPENDIX I

The gas chromatograph was calibrated with two independently prepared standards as follows: 50 mg of TDI was weighed to the nearest 0.1 mg and diluted to 50 ml with hexane. A 10-ml aliquot of each standard solution was mixed with 5 ml of hexadecane internal standard solution (0.5 mg/ml in hexane) and was diluted to 50 ml with hexane. Standards were injected after every third sample injection to maintain calibration.

The analysis results were calculated from relative response factors (RRF) computed from electronically integrated peak areas of the standards using the following equations:

$$RRF = \frac{\text{mg/ml Test Chemical x Peak Area of Internal Standard}}{\text{Peak Area of Test Chemical x mg/ml of Internal Standard}}$$

then the mg/g chemical in the vehicle was calculated as,

$$\text{mg/g Chemical} = \frac{\text{RRF x Sample Peak Area x mg/ml Internal Standard x D.F.}}{\text{Peak Area Internal Standard x Grams of Sample}}$$

where D.F. = dilution factor

The linearity of the chromatograph detector response was evaluated with solutions of TDI in hexane at concentrations of 0.115, 0.192, and 0.230 mg/ml. The correlation coefficient was 0.9992. The test results are shown on the Tables 11-13 and Figure 13.

TABLE II. TOLUENE DIISOCYANATE STABILITY IN CORN OIL: ZERO TIME ANALYSES

Dosage Level (mg/ml)	Corn Type	mg TDI/ml (Theoretical)	mg TDI/ml (Found)	Percent Recovery (Found/Theoretical x 100)
9	Dry	8.97	9.15	102.0
		9.03	8.86	98.1
				$\bar{x}$ = 100.1 ± 2.1
9	Normal	8.60	8.24	95.8
		9.05	8.97	99.1
				$\bar{x}$ = 97.5 ± 1.7
36	Dry	36.80	37.45	101.8
		36.72	36.18	98.5
				$\bar{x}$ = 100.2 ± 1.7
36	Normal	36.52	35.50	97.2
		36.53	36.86	100.9
				$\bar{x}$ = 99.1 ± 1.9
72	Dry	72.38	72.41	100.0
		72.58	72.11	99.4
				$\bar{x}$ = 99.7 ± 0.3
72	Normal	73.18	71.57	97.8
		72.85	71.68	98.4
				$\bar{x}$ = 98.1 ± 0.3

(a) The mean water content of the dry and normal corn oil used for the stability study was 0.0053% and 0.0500%, respectively. Water analyses could not be run on the TDI-corn oil blends because TDI reacts with Karl-Fischer reagent.

TABLE I2. TOLUENE DIISOCYANATE STABILITY IN CORN OIL: 24-HOUR STABILITY ANALYSES

Dosage Level (mg/ml)	Corn Type	mg TDI/ml (Theoretical)	mg TDI/ml (Found)	Percent Recovery (Found/Theoretical x 100)
9	Dry	8.97	7.44	82.9
		9.03	8.05	89.1
				$\bar{x}$ = 86.0 ± 3.1
9	Normal	8.60	6.26	72.8
		9.05	6.85	75.7
				$\bar{x}$ = 74.3 ± 1.5
36	Dry	36.80	34.11	92.7
		36.72	33.41	91.0
				$\bar{x}$ = 91.9 ± 0.9
36	Normal	36.52	29.29	80.2
		36.53	30.30	82.9
				$\bar{x}$ = 81.6 ± 1.4
72	Dry	72.38	69.27	95.7
		72.58	65.81	90.7
				$\bar{x}$ = 93.2 ± 2.5
72	Normal	73.18	64.35	87.9
		72.85	63.63	87.3
				$\bar{x}$ = 87.6 ± 0.3

TABLE I3. TOLUENE DIISOCYANATE STABILITY IN CORN OIL: 7-DAY STABILITY ANALYSES

Dosage Level (mg/ml)	Corn Type	mg TDI/ml (Theoretical)	mg TDI/ml (Found)	Percent Recovery (Found/Theoretical x 100)
9	Dry	8.97	4.42	49.3
		9.03	4.21	46.6
				$\bar{x}$ = 48.0 ± 1.4
9	Normal	8.60	1.76	20.5
		9.05	lost	lost
36	Dry	36.80	25.11	68.2
		36.72	24.79	67.5
				$\bar{x}$ = 67.9 ± 0.4
36	Normal	36.52	17.69	48.4
		36.53	19.65	53.8
				$\bar{x}$ = 51.1 ± 2.7
72	Dry	72.38	57.91	80.0
		72.58	59.07	81.4
				$\bar{x}$ = 80.7 ± 0.7
72	Normal	73.18	53.57	73.2
		72.85	52.43	72.0
				$\bar{x}$ = 72.6 ± 0.6

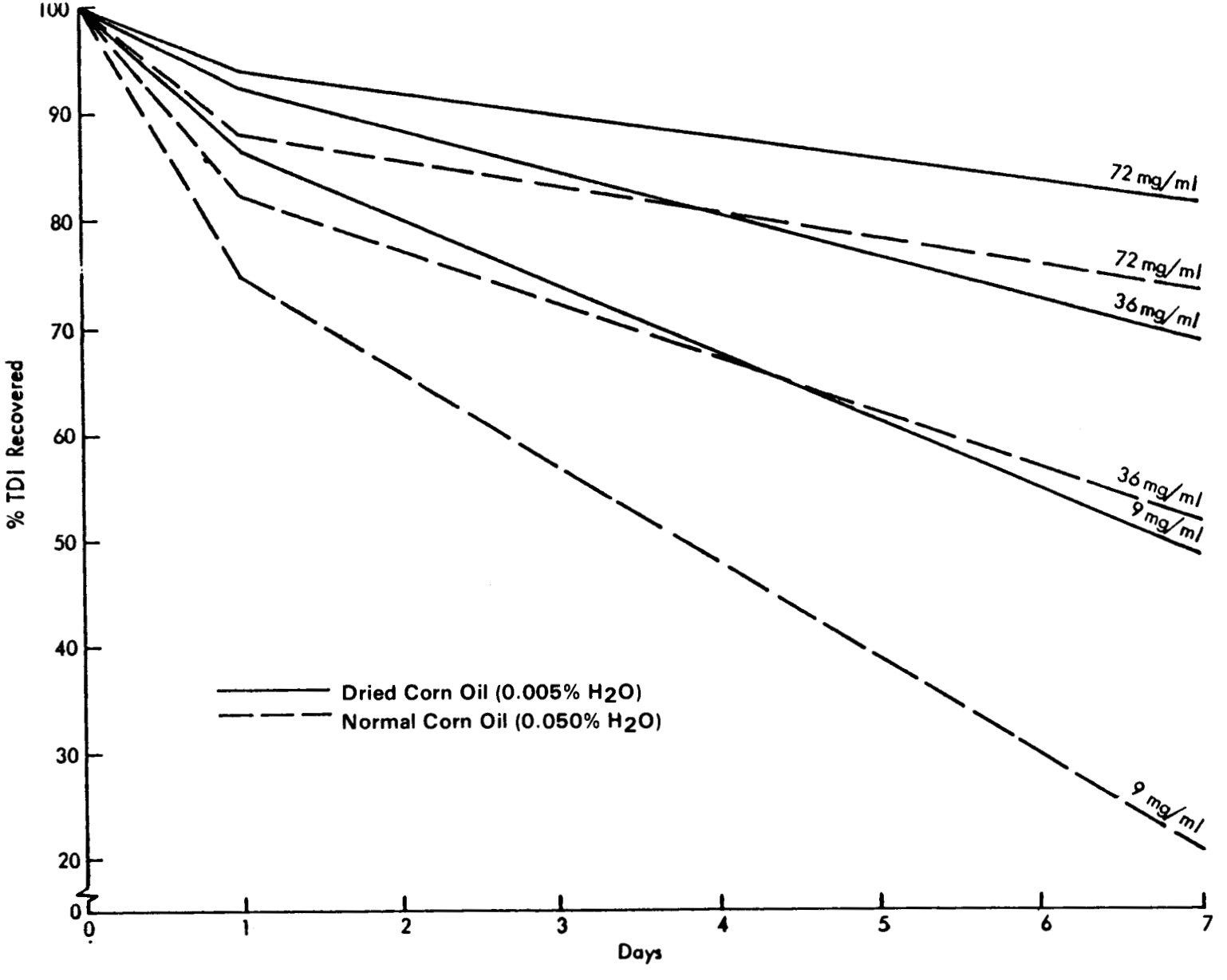

Figure 13. Stability of Toluene Diisocyanate in Normal and Dried Corn Oil at 25°C

4. Discussion

During the stability study, the gavage samples were inspected daily. All of the samples prepared with the dried oil remained clear over the 7-day period, and all of the hexane dilutions prepared from these samples for GC analysis were also free of insoluble matter.

The gavage solutions prepared with the "normal corn oil" remained clear for the first 24 hours, but showed evidence of insoluble matter after 48 hours. All of the hexane dilutions prepared from the "normal oil" samples exhibited a white precipitate in proportion to the dose level, except the zero time samples. Since no precipitate was observed in the gavage solutions prepared with dried corn oil, one can infer that the precipitate observed in the normal oil samples was probably caused by reaction products of TDI with water.

"Wet" corn oil containing 0.05% water corresponds to 25.4 μmol water/ml corn oil (0.916 g ml x 0.0005/18 = 25.4); whereas, "dry" corn oil with 0.0053% water corresponds to 3.5 μmol water ml corn oil. One mole of water will consume two moles of TDI. Therefore, the water in one ml of "wet" corn oil will react with 50.8 μmol of TDI and "dry" will react with 5.4 μmol. The following table summarizes the amount of TDI consumed at each dose level.

Dose mg/ml (mol)	Percent TDI that reacts with Water			
	Wet Corn Oil		Dry Corn Oil	
	Theo. *(a)*	Act. *(b)*	Theo.	Act.
9.0 (51.7)	98.3	79.5	10.4	52.0
36.0 (206.8)	24.6	48.9	2.6	32.1
72.0 (413.6)	12.3	27.4	1.3	19.3

(a) Calculated
(b) From this study

It is evident that the amount of water present in normal ("wet") corn oil is sufficient to account for 45%-100% of the decomposition of TDI observed in this study. The "dry" corn oil theoretical values can only account for 6%-20% of the actual observed results. Even if the dry corn oil absorbed enough water to approach the day one value of 0.0128%, this would still only account for 16%-46% of the observed results. Thus, it is obvious that TDI must also react with components of the corn oil other than water, but the dry corn oil appears to be more destructive than the normal material.

A literature study of the possible decomposition of TDI in corn oil was conducted by Midwest Research Institute. Besides the reaction of TDI with water in the corn oil to form aromatic amines and disubstituted urea, TDI could also react with the sterols, tocopherols, and triterpene alcohols contained in the corn oil; it is most likely the remaining loss of TDI was due to dimer formation, but this was not experimentally determined.

5. Conclusions

Toluene diisocyanate (TDI) was unstable in gavage solutions prepared with corn oil of normal moisture content (0.05%) and with corn oil which had been dried to a water content of 0.005%. After 7 days storage at room temperature, gavage solutions in normal corn oil at dose levels of 9, 36, and 72 mg/ml showed losses of 80%, 49%, and 27%, respectively. Gavage solutions prepared at the 9, 36, and 72 mg/ml dose levels with the dried corn oil showed losses of 52%, 32%, and 19% respectively after 7 days at room temperature.

An evaluation of stability test results revealed that over 90% of the TDI loss measured in the gavage solutions prepared with dried corn oil was caused by reaction of TDI with components in the corn oil other than water. The same calculations applied to gavage solutions prepared with normal corn oil showed that 12%-98% of the loss could have been caused by reaction with the available water in the oil (theoretical basis) and the remainder was due to reaction of TDI with components of the corn oil.

APPENDIX J

ANALYSIS OF CORN OIL FOR WATER CONTENT

APPENDIX J

A. SAMPLE IDENTIFICATION AND ANALYSIS RESULTS

Two 4 oz bottles of corn oil were received from Litton Bionetics on 8/24/79 identified as follows:

1. Corn oil, 8/23/79, LBI No. 4313, Lab No. RO-4325-S79
2. Corn oil, 8/23/79, LBI No. 4332, Lab No. RO-4326-S79

The samples were analyzed by the Karl Fischer method using chloroform/methanol (3/1) as the titrating medium. For purposes of comparison, the corn oil currently being used at MRI for conducting gavage stability studies (Mazola® food grade corn oil) was run along with the samples.

WATER CONTENT OF CORN OIL SAMPLES (as Percent H_2O)

Litton No. 4313	Litton No. 4332	MRI Oil
0.069	0.061	0.047
0.070	0.060	0.043
0.068	0.058	0.045
$\bar{x}$ = 0.069 ± 0.001	0.060 ± 0.002	0.045 ± 0.002

B. DISCUSSION

The moisture content of the two oil samples from Litton Bionetics was significantly higher than that of the MRI sample included for comparison purposes. However, according to Mr. Jack Ackerboom, Director of Research at Corn Products Company Research Center in Princeton, New Jersey, these samples are within the range of moisture content for typical Mazola® oil, although they are on the high side of the range. According to Mr. Ackerboom, the average moisture content of Mazola® oil will be around 0.05%.

If it is necessary to dry corn oil prior to preparing gavage solutions, the recommended procedure is to heat the oil to 135°C in a glass vessel while bubbling dry nitrogen through it for about 30 minutes. Heating the oil to 135°C under a vacuum with a dry nitrogen sweep would be the ideal method, according to Mr. Ackerboom.

C. CONCLUSION

Two samples of corn oil from Litton Bionetics showed moisture contents of 0.060% and 0.069% by the Karl Fischer method. While these values fell within the normal moisture range for Mazola oil (average 0.05% according to the manufacturer), they favored the high end of the range and were significantly higher than the moisture content (0.045%) of corn oil used at MRI for gavage stability studies.

APPENDIX K

ANALYSIS OF TOLUENE DIISOCYANATE/CORN OIL MIXTURES FOR CONCENTRATIONS OF TOLUENE DIISOCYANATE

APPENDIX K

A. METHOD A

A few drops of corn oil suspension, accurately weighed, were diluted with benzene to a suitable volume. The solution was analyzed by gas chromatography on a Varian Model 2100 instrument equipped with flame ionization detectors. The column used was 1.8 m x 2 mm I.D. glass packed with 3% OV-1 on 80 100 mesh Supelcoport. The column temperature was 105° with a nitrogen (carrier) flow rate of 34 ml minute. Concentrations were determined by analysis of standard solution of toluene diisocyanate in benzene under the same parameters.

The recovery study was performed by weighing accurately a few drops of control corn oil and adding an amount of the test compound in benzene equivalent to the theoretical concentration of the dosage solutions. The recovery sample was then diluted to a suitable volume with benzene and analyzed as described above.

In both instances, the concentration of test compound was determined as mg per gram of corn oil. This value was converted to gm per ml of corn oil using its density value of 0.918 gm/ml.

B. METHOD B

A 2.0-ml aliquot of the corn oil dosage mixture was extracted with 20 ml of acetonitrile containing biphenyl as an internal standard (1 mg/ml). Analysis of the extract was performed by the gas chromatography system described below:

Instrument: Hewlett Packard 5880A or 5840A equipped with a 7672 Automatic Sampler

Column: 3% OV-17 on 80/100 mesh Supelcoport, 1.8 m x 2 mm I.D., glass, silanized

Detector: Flame ionization

Temperature: Oven, 120°C, isothermal
Injector, 240°C
Detector, 280°C

Carrier gas: Nitrogen

Flow rate: 30 ml/min

The concentration of the test compound was determined by reference to a calibration curve prepared by analysis of a set of TDI working standards.

C. RESULTS: See Table K1

TABLE K1. ANALYSES OF CORN OIL MIXTURES

Date Mixed	Concentration (a) of Toluene Diisocyanate in Corn Oil for Target Concentration (mg/ml)			
	9	18	36	72
Method A				
2/05/79	3.9	10.0	24.7	-
3/01/79	5.9	12.5	34.0	58.8
3/22/79	-	-	-	46.3
Method B				
8/23/79	7.0	-	-	-
9/06/79	-	-	-	72.8
9/20/79	-	16.2	-	-
10/04/79	8.3	-	31.6	-
10/04/79	8.0	-	37.9	-
11/01/79	5.6	12.4	29.1	62.9
11/15/79	-	15.2	-	32.8
11/29/79	-	-	34.9	-
12/13/79	8.2	-	-	-
12/27/79	-	-	-	70.2
1/09/80	5.8	13.0 (17.0, MRI)	-	-
1/24/80	-	-	33.1	-
2/07/80	6.9	-	-	-
2/21/80	-	-	-	67.2
3/06/80	-	15.8	-	-
3/20/80	-	-	30.8	-
5/15/80	-	-	33.4	-
6/12/80	8.0	-	-	66.6
6/26/80	-	17.8	-	-
7/10/80	-	-	33.0	-
7/24/80	7.6	-	-	-
8/07/80	-	-	-	66.4
8/21/80	-	17.8	-	-
9/04/80	-	-	32.4	-
9/18/80	7.8	-	-	-
10/17/80	-	14.7	-	-
10/30/80	-	-	30.5	-
11/04/80	-	-	36.5	- (66.8, MRI)
11/30/80	-	-	-	64.0
12/11/80	-	17.3	-	-
12/24/80	-	-	31.6	-
Mean (mg/ml)	6.9	14.8	32.4	60.8
Standard deviation	1.4	2.5	3.2	12.2
Coefficient of variation (%)	19.7	17.2	10.0	20.1
Range (mg/ml)	3.9-8.3	10.0-17.8	24.7-37.9	32.8-72.8
No. of samples	11	11	14	10

(a) The data presented are the average of the results of duplicate analyses. Only values verified in the data audit are presented.

APPENDIX L

MUTAGENICITY OF TOLUENE DIISOCYANATE IN SALMONELLA

TABLE L1. MUTAGENICITY OF TOLUENE DIISOCYANATE (2,4 AND 2,6-MIXTURE) IN SALMONELLA (CAS# 26471-62-5)

Strain	Dose (μg/plate)	Revertants/plate *(a)* -S9	+S9 (rat)	+S9 (hamster)
TA100	0	170 ± 2.6	99 ± 0.3	95 ± 5.3
	3		102 ± 3.0	109 ± 3.9
	10	157 ± 8.5	118 ± 15.4	97 ± 9.6
	33	138 ± 10.5	144 ± 15.3	118 ± 6.4
	100	132 ± 16.0	159 ± 12.7	143 ± 6.1
	333	111 ± 6.7 ppt *(b)*	178 ± 6.0	134 ± 4.4
	1000	145 ± 17.5 ppt		
	3333			
	10000			
TA1535	0	26 ± 6.4	14 ± 5.5	10 ± 2.3
	10	25 ± 2.4		
	33	20 ± 1.9		
	100	17 ± 1.9	19 ± 4.5	11 ± 2.2
	333	15 ± 3.8 ppt	20 ± 3.5	14 ± 6.1
	1000	12 ± 1.3 ppt	22 ± 7.7	11 ± 2.1
	3333		14 ± 2.3 ppt	7 ± 1.7 ppt
	10000		9 ± 2.0 ppt	3 ± 2.7 ppt
TA1537	0	5 ± 1.2	14 ± 1.9	4 ± 0.9
	10	8 ± 0.9		
	33	11 ± 1.5		
	100	8 ± 2.4	20 ± 2.6	15 ± 1.0
	333	12 ± 2.0 ppt	17 ± 5.1	19 ± 2.7
	1000	8 ± 1.2 ppt	20 ± 2.3	14 ± 1.2
	3333		7 ± 1.2 ppt	14 ± 1.5 ppt
	10000		8 ± 0.9 ppt	8 ± 0.9 ppt
TA98	0	19 ± 1.5	20 ± 1.3	31 ± 3.8
	3		21 ± 2.6	35 ± 1.0
	10	17 ± 4.9	25 ± 0.7	31 ± 4.1
	33	20 ± 3.5	30 ± 4.0	34 ± 8.4
	100	17 ± 2.2	52 ± 0.6	58 ± 7.3
	333	14 ± 1.2 ppt	67 ± 0.9	97 ± 8.6
	1000	16 ± 2.8 ppt		

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

(b) Precipitate observed.

TABLE L2. MUTAGENICITY OF 2,6-TOLUENE DIISOCYANATE (CAS# 91-08-7) IN SALMONELLA

Strain	Dose (μg/plate)	Revertants/plate *(a)* -S9	+S9 (rat)	+S9 (hamster)
TA100	0	97 ± 4.6	162 ± 5.8	162 ± 14.4
	3		156 ± 18.6	189 ± 4.7
	10	96 ± 6.1	178 ± 5.1	212 ± 4.2
	33	93 ± 5.7	202 ± 2.0	261 ± 7.4
	100	97 ± 3.5	251 ± 8.8	312 ± 4.9
	333	91 ± 1.7 ppt *(b)*	253 ± 17.8 ppt	327 ± 4.9 ppt
	666	95 ± 7.8 ppt		
TA1535	0	8 ± 2.2	8 ± 1.3	9 ± 2.5
	10	6 ± 0.9		
	33	7 ± 1.2		
	100	6 ± 0.9	8 ± 1.3	9 ± 0.3
	333	7 ± 0.7 ppt	7 ± 0.6 ppt	9 ± 0.7 ppt
	666	9 ± 1.8 ppt		
	1000		5 ± 1.5 ppt	4 ± 1.8 ppt
	3333		3 ± 0.7 ppt	5 ± 1.5 ppt
	10000		5 ± 1.5 ppt	5 ± 1.9 ppt
TA1537	0	102 ± 16.2	185 ± 8.5	175 ± 6.2
	10	135 ± 0.9		
	33	118 ± 7.9		
	100	97 ± 10.1	156 ± 10.5	184 ± 10.3
	333	112 ± 4.5 ppt	143 ± 25.7 ppt	223 ± 17.6 ppt
	666	91 ± 9.8 ppt		
	1000		115 ± 22.9 ppt	150 ± 13.2 ppt
	3333		121 ± 17.3 ppt	193 ± 8.2 ppt
	10000		124 ± 21.5 ppt	116 ± 51.1 ppt
TA98	0	12 ± 2.1	31 ± 0.9	38 ± 2.3
	3		35 ± 3.2	60 ± 5.1
	10	10 ± 1.7	50 ± 8.5	75 ± 1.5
	33	11 ± 1.9	65 ± 0.9	117 ± 7.1
	100	10 ± 2.6	84 ± 0.3	155 ± 5.0
	333	14 ± 2.5 ppt	106 ± 6.8 ppt	170 ± 12.3 ppt
	666	16 ± 1.2 ppt		

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

(b) Precipitate observed.

APPENDIX M
DATA AUDIT SUMMARY

APPENDIX M

DATA AUDIT SUMMARY

The experimental data and summary tables of the NTP Technical Report No. 251 on the toxicology and carcinogenesis studies of commercial grade 2,4- and 2,6-toluene diisocyanate were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. An audit of the data was conducted by Immuquest Laboratories, Inc. under a contract for NTP (N01-ES-38947). The individuals involved in the audit were P.H. Errico, M.A.; L.H. Brennecke, D.V.M.; C.S. Reese, M.S.; and K.M. Witkin, Ph.D. The two-year chronic studies in rats and mice were begun in December, 1978 and completed in January, 1981, at Litton Bionetics, Inc., Kensington, Maryland, under a subcontract with Tracor Jitco, Inc.

The full report of the NTP audit is on file at the National Toxicology Program, NIEHS, and is available upon request. The audit included, but was not limited to, a review of the records of the in-life portion of the studies for 10% of the animals, 100% of the available chemistry data, and a random 50% sample of the chemical mix calculations. All Individual Animal Data Records were examined for correspondence between necropsy observations and histopathologic findings. All wet tissue bags were counted and 10% were reviewed for animal identification and the presence of untrimmed lesions. A complete slide-block match for both sexes of both species in the high dose and control groups was performed.

The audit indicated there were some gross observations suggesting possible tumors but with no correlation of microscopic diagnoses. These included 7 gross lesions in treated animals and 1 gross lesion in controls that had not been trimmed. Mortality records indicated that two more mice and five more rats may have died from gavage trauma. The accuracy of the TDI dose mixtures were uncertain because of reactivity with water and the unknown nature of the decomposition products that resulted from preparation of the TDI-corn oil mixtures. Although not every potential discrepancy identified in the audit was fully resolved it was concluded that the data reported were adequate to support the conclusions presented in this Technical Report.

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