NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 289

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZENE

(CAS NO. 71-43-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZENE

(CAS NO. 71-43-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

April 1986

NTP TR 289

NIH Publication No. 86-2545

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

NOTE TO THE READER

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

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

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.

- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.

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

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

- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

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

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

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

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

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

CONTENTS

CONTENTS (Continued)

TABLES

TABLES (Continued)

FIGURES

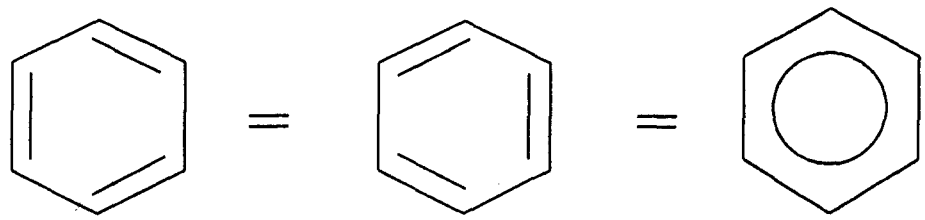
APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)

APPENDIXES (Continued)

APPENDIXES (Continued)



BENZENE

Benzol, Cyclohexatriene, Pyrobenzol

C_6H_6 MW = 78.11

C = 92.25% H = 7.75%

CAS No. 71-43-2

ABSTRACT

During the 17-week studies, groups of 10 or 15 male and female F344/N rats and B6C3F$_1$ mice were gavaged 5 days per week with benzene in corn oil (5 ml/kg) at doses of 0 to 600 mg/kg. No benzene-related deaths occurred; in rats that received benzene, final mean body weights were 14%-22% lower compared with vehicle controls and in mice, slight dose-related reductions were observed (less than 10% differences). Doses for the 2-year studies were selected based on clinical observations (tremors in higher dosed mice), on clinical pathologic findings (lymphoid depletion in rats and leukopenia in mice), and on body weight effects.

Two-year toxicology and carcinogenesis studies of benzene (greater than 99.7% pure) were conducted in groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex and for each dose. Doses of 0, 50, 100, or 200 mg/kg body weight benzene in corn oil (5 ml/kg) were administered by gavage to male rats, 5 days per week, for 103 weeks. Doses of 0, 25, 50, or 100 mg/kg benzene in corn oil were administered by gavage to female rats and to male and female mice for 103 weeks. Ten additional animals in each of the 16 groups were killed at 12 months and necropsies were performed. Hematologic profiles were performed at 3-month intervals. These studies were designed and conducted because of large production volume and potential human exposure, because of the epidemiologic association with leukemia, and because previous experiments were considered inadequate or inconclusive for determining potential carcinogenicity in laboratory animals.

In the 2-year studies, mean body weights of the 200 mg/kg male rats (−23%) and the 100 mg/kg mice (−14% to −19%) were lower than those of the vehicle controls, and survival of dosed groups decreased with increasing dose (rats--male: vehicle control, 32/50; low dose, 29/50; mid dose, 25/50; high dose, 16/50; female: 46/50; 38/50; 34/50; 25/50; mice--male: 28/50; 23/50; 18/50; 7/50; female: 30/50; 26/50; 24/50; 18/50). At week 92 for rats and week 91 for mice, survival was greater than 60% in all groups; most of the dosed animals that died before week 103 had neoplasia.

Compound-related nonneoplastic or neoplastic effects on the hematopoietic system, Zymbal gland, forestomach, and adrenal gland were found both for rats and mice. Further, the oral cavity was affected in rats, and the lung, liver, harderian gland, preputial gland, ovary, and mammary gland were affected in mice. Significantly increased ($P < 0.05$) incidences of neoplasms were observed at multiple sites for male and female rats and for male and female mice. Primary neoplasms observed in rats and mice are summarized in Table 1.

TABLE 1. SUMMARY OF PRIMARY NEOPLASMS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Rats			Mice	
	Male	Female		Male	Female
Zymbal gland	+	+	Zymbal gland	+	+
Oral cavity	+	+	Lymphoma	+	+
Skin	+	–	Lung	+	+
			Harderian gland	+	±
			Mammary gland	–	+
			Preputial gland	+	NA
			Forestomach	±	±
			Ovary	NA	+
			Liver	–	±

\+ = Increase relative to vehicle controls
± = Marginal increase relative to vehicle controls
– = No difference from vehicle controls
NA = Not applicable

Hematologic data from vehicle control and dosed rats and mice were obtained at 3-month intervals from 0 to 24 months. Reliably identifiable hematologic effects were limited to lymphocytopenia and associated leukocytopenia in benzene-dosed rats and mice. These effects were seen from 3 to 18 months in dosed male rats and in dosed male mice; a similar but less pronounced response was observed in dosed female rats during this same time period. The effect in female mice was limited to 12-18 months. The technical quality of certain of these data was questionable; thus, more detailed analyses (e.g., investigation of the association between hematologic and pathologic changes) are deemed inappropriate for these data. Benzene increased the frequency of micronucleated normochromatic peripheral erythrocytes in male and female mice (rats were not examined); males were more sensitive than females.

The hematopoietic system of rats and mice of each sex was affected by benzene in the 2-year studies. The incidences of malignant lymphomas in all dosed groups of mice were greater than those in the vehicle controls (male: 4/49; 9/48; 9/50; 15/49; female: 15/49; 24/45; 24/50; 20/49). Lymphoid depletion of the splenic follicles (rats) and thymus (male rats) was observed at increased incidences. Bone marrow hematopoietic hyperplasia was observed at increased incidences in dosed mice of each sex (male: 0/49; 11/48; 10/50; 25/49; female: 3/49; 14/45; 8/50; 13/49).

The incidences of Zymbal gland carcinomas in mid and high dose male rats and in dosed female rats were greater than those in the vehicle controls (male: 2/32; 6/46; 10/42; 17/42; female: 0/45; 5/40; 5/44; 14/46). The incidences of Zymbal gland carcinomas in mid and high dose male mice and in high dose female mice were greater than those in the vehicle controls (male: 0/43; 1/34; 4/40; 21/39; female: 0/43; 0/32; 1/37; 3/31). In mid and high dose male mice and in high dose female mice, the incidences of epithelial hyperplasia of the Zymbal gland were also increased (male: 0/43; 3/34; 12/40; 10/39; female: 1/43; 1/32; 2/37; 6/31).

Hyperplasia of the adrenal capsule was observed at increased incidences in dosed mice of each sex (male: 2/47; 32/48; 14/49; 4/46; female: 5/49; 19/44; 34/50; 30/48). The incidence of pheochromocytomas in mid dose male mice was greater than that in the vehicle controls (male: 1/47; 1/48; 7/49; 1/46), whereas the incidences in dosed female mice were lower than that in the vehicle controls (female: 6/49; 1/44; 1/50; 1/48). Hyperplasia of the zona fasciculata of the adrenal cortex was observed at increased incidences in low dose rats of each sex (male: 0/50; 13/49; 0/48; 2/49; female: 0/50; 17/50; 0/47; 0/49).

Benzene was associated with increased incidences of neoplasms of the skin and oral cavity of rats. The incidences of squamous cell papillomas and squamous cell carcinomas of the skin in high dose male rats were greater than those in the vehicle controls (squamous cell papilloma: 0/50; 2/50; 1/50; 5/50; squamous cell carcinoma: 0/50; 5/50; 3/50; 8/50). Increased incidences of uncommon squamous cell papillomas or squamous cell carcinomas (combined) of the oral cavity were observed in dosed male and female rats (male: 1/50; 9/50; 16/50; 19/50; female: 1/50; 5/50; 12/50; 9/50). Incidences of squamous cell papillomas or carcinomas (combined) (male: 2/45; 2/42; 3/44; 5/38; female: 1/42; 3/40; 6/45; 5/42), hyperkeratosis, and epithelial hyperplasia of the forestomach were increased in some dosed groups of male and female mice; incidences of hyperkeratosis and acanthosis were increased in high dose male rats.

Compound-related effects in the lung, harderian gland, preputial gland, ovary, mammary gland, and liver were seen in mice but not in rats. Administration of benzene was associated with increased incidences of alveolar epithelial hyperplasia in mid and high dose mice (male: 2/49; 3/48; 7/50; 10/49; female: 1/49; 1/42; 9/50; 6/49). Increased incidences of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) were observed in high dose male mice (carcinomas: 5/49; 11/48; 12/50; 14/49; adenomas or carcinomas: 10/49; 16/48; 19/50; 21/49). Alveolar/bronchiolar adenomas were seen at increased incidences in high dose female mice (4/49; 2/42; 5/50; 9/49), as were alveolar/bronchiolar carcinomas (0/49; 3/42; 6/50; 6/49) and alveolar/bronchiolar adenomas or carcinomas combined (4/49; 5/42; 10/50; 13/49) in mid and high dose female mice.

The incidences of focal or diffuse hyperplasia of the harderian gland were increased in dosed mice of each sex (male: 0/49; 5/46; 11/49; 7/48; female: 6/48; 10/44; 11/50; 10/47). The incidences of harderian gland adenomas (0/49; 9/46; 13/49; 11/48) in dosed male mice were greater than that in the vehicle controls. A marginal increase in the incidence of adenomas or carcinomas (combined) of the harderian gland was seen in high dose female mice (5/48; 6/44; 10/50; 10/47).

The administration of benzene to male mice was associated with increased incidences of hyperplasia (1/21; 18/28; 9/29; 1/35) and squamous cell carcinomas (0/21; 3/28; 18/29; 28/35) of the preputial gland. Increased incidences of mammary gland carcinomas were found in mid dose and high dose female mice (0/49; 2/45; 5/50; 10/49) and carcinosarcomas in high dose female mice (0/49; 0/45; 1/50; 4/49).

Increased incidences of various uncommon neoplastic and nonneoplastic lesions of the ovary (papillary cystadenoma, luteoma, granulosa cell tumor, tubular adenoma, benign mixed tumor, epithelial hyperplasia, and senile atrophy) were associated with administration of benzene to female mice. In mid and high dose female mice, the incidences of granulosa cell tumors (1/47; 1/44; 6/49; 7/48) and benign mixed tumors (0/47; 1/44; 12/49; 7/48) were greater than those in the vehicle controls.

Increased incidences of hepatocellular adenomas were observed in low dose female mice (1/49; 8/44; 5/50; 4/49) and hepatocellular adenomas or carcinomas (combined) in low dose and mid dose female mice (4/49; 12/44; 13/50; 7/49).

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

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** of benzene for male F344/N rats, for female F344/N rats, for male B6C3F$_1$ mice, and for female B6C3F$_1$ mice. For male rats, benzene caused increased incidences of Zymbal gland carcinomas, squamous cell papillomas and squamous cell carcinomas of the oral cavity, and squamous cell papillomas and squamous cell carcinomas of the skin. For female rats, benzene caused increased incidences of Zymbal gland carcinomas and squamous cell papillomas and squamous cell carcinomas of the oral cavity. For male mice, benzene caused increased incidences of Zymbal gland squamous cell carcinomas, malignant lymphomas, alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined), harderian gland adenomas, and squamous cell carcinomas of the preputial gland. For female mice, benzene caused increased incidences of malignant lymphomas, ovarian granulosa cell tumors, ovarian benign mixed tumors, carcinomas and carcinosarcomas of the mammary gland, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and Zymbal gland squamous cell carcinomas. Dose-related lymphocytopenia was observed for male and female F344/N rats and male and female B6C3F$_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzene is based on the 17-week studies that began in October 1978 and ended in February 1979 and on the 2-year studies that began in December 1979 and ended in December 1981 at Battelle Columbus Laboratories.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

James Huff, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Rajendra S. Chhabra, Ph.D.
David M. DeMarini, Ph.D.
Joseph K. Haseman, Ph.D.
W.M. Kluwe, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
Bernard A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on Rats on 2/15/83)

Gary A. Boorman, D.V.M., Ph.D. (NTP) (Chair)
S. Eustis, D.V.M., Ph.D. (NTP)
R. Kovatch, D.V.M. (Program Resources, Inc.)
W. Macklin, D.V.M., Ph.D. (Burroughs Wellcome)
H. Solleveld, D.V.M., Ph.D. (NTP)
M. Wolfe, D.V.M., Ph.D. (NTP)

(Evaluated Slides and Prepared Pathology Report on Mice on 3/11/83)

S. Eustis, D.V.M., Ph.D. (NTP) (Chair)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
R. Kovatch, D.V.M. (Program Resources, Inc.)
W. Macklin, D.V.M., Ph.D. (Burroughs Wellcome)
H. Solleveld, D.V.M., Ph.D. (NTP)

(Evaluated Hematology Data on Rats and Mice on 5/2/84)

Robert Maronpot, D.V.M. (NTP) (Chair)
Richard Irons, D.V.M., Ph.D.
Chemical Industry Institute of Toxicology
Gary Kociba, D.V.M., Ph.D.
Ohio State University
Walter Loeb, D.V.M., Ph.D.
Litton Bionetics, Inc.
Alan Rebar, D.V.M., Ph.D.
Purdue University
Morrow Thompson, D.V.M., Ph.D. (NTP)

Principal Contributors at Battelle Columbus Laboratories
(Conducted Studies and Evaluated Tissues)

A. Peters, D.V.M., Principal Investigator
E. Leighty, Ph.D., Chemist
R. Persing, Pathologist (Rats)
S. Summer, B.S., Chemist
T. Voss, M.S., Operations Supervisor
C. Chrisp, Pathologist (Mice)

Principal Contributors at Experimental Pathology Laboratory
(Provided Pathology Quality Assurance)

Deborah Banas, D.V.M., M.S.
J. Gauchat, Pathology Coordinator

Principal Contributors at Program Resources, Inc.
(Provided Statistical Analyses of Hematology Data)

Steven K. Seikop, M.S.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D., Project Manager
Abigail C. Jacobs, Ph.D., Senior Scientist
John Warner, M.S., Chemist/Statistician

PEER REVIEW PANEL (October 28, 1983)

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

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

James Swenberg, D.V.M., Ph.D.
(Principal Reviewer)
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D. (Principal Reviewer)
Board on Toxicology and Environmental Health Hazards
National Academy of Sciences
Washington, D.C.

Robert M. Elashoff, Ph.D. (Principal Reviewer)
University of California at Los Angeles
Jonsson Comprehensive Cancer Center
Los Angeles, California

Seymour L. Friess, Ph.D. (Principal Reviewer)
Arlington, Virginia

J. Michael Holland, Ph.D., D.V.M.
Chevron Environmental Health Center
Richmond, California

Robert A. Scala, Ph.D.
Exxon Corporation
East Millstone, New Jersey

Tom Slaga, Ph.D.*
Science Park, Research Division
University of Texas System Cancer Center
Smithville, Texas

John R. Van Ryzin, Ph.D.
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

Stan D. Vesselinovitch, Ph.D.*
Professor, Departments of Radiology and Pathology
University of Chicago
Chicago, Illinois

Mary Vore, Ph.D.*
Assistant Professor
Pharmacology Department
University of Kentucky
College of Medicine
Lexington, Kentucky

* Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZENE (October 28, 1983 Meeting)

On October 28, 1983, the draft Technical Report on the toxicology and carcinogenesis studies of benzene received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The 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.

Dr. Friess, a principal reviewer, essentially agreed with the conclusions. He added that the findings of leukopenia in rats and mice could be cited in the conclusions, and a summary table in the results section would be useful for highlighting the 17-week and 2-year studies. To aid reviewers in interpretation of findings where significance shown by life table analysis differs from that shown by the incidental tumor test, Dr. Friess asked that more explanation be given and perhaps, where appropriate, values from the Fisher exact test and Cochran-Armitage trend test could be included in summary tables. Dr. J. Huff, NTP, noted that the results of the latter two tests are included routinely in the statistical analyses appendix but since NTP emphasizes survival-adjusted methods, only these analyses are generally included in the Results. Dr. Friess also suggested that the discussion on the role of benzene metabolites and putative precursors in benzene carcinogenesis be condensed and made less speculative.

As a second principal reviewer, Dr. Swenberg agreed with the conclusions; however, he suggested that the maximum tolerated dose (MTD) was exceeded in the high dose male rats. Like Dr. Friess, he thought this was an important bioassay of a widely used chemical and there was little question that benzene was carcinogenic in these studies. He said that general comments needed to be made to provide more emphasis for the route of administration (gavage), since the routes relevant to human exposure were mainly inhalation and dermal. Dr. Swenberg's critique focused on two areas: a need for editing and reorganizing the manuscript, and a more complete presentation of the hematologic data. Dr. Huff proposed that consideration of the hematologic data be deferred and the present discussion concentrate on the carcinogenicity of benzene, since the hematologic data may not have been adequately analyzed and appeared to be somewhat inconsistent.

As a third principal reviewer, Dr. Davis also agreed with the conclusions and said the report provided a good analysis of the carcinogenicity data. She stated that a more detailed discussion of reproductive and chromosomal effects was needed and the information on epidemiologic studies, human exposure, and production patterns could be expanded. She said the hematologic data were not essential to the study.

As a fourth principal reviewer, Dr. Elashoff agreed with the conclusions. He stated that, for some tumor sites specified in the conclusions, statistical significance depended on the test used; the discussion section therefore should contain the rationale for using a particular test for a given site. In view of the multiple sex/species/tumor sites, he recommended including in the Discussion summary tables of response data which would indicate significant findings. He discussed and attached a series of such tables to his review. Dr. Elashoff noted the patterns of late mortality with most animals dying after 90 weeks (rats) or 95 weeks (mice), and emphasized that survival was good to that time and the cause of death was likely associated with the neoplasms.

In discussion by the Panel, Dr. Scala stated that there should be more balance in the Discussion section of the report on the metabolism of benzene and that the in-depth description of genetic toxicology information could be enhanced with a summary table. Dr. Davis noted that significant nontumor

toxic effects might be included in the Abstract. Dr. Hook noted a consensus for inclusion of noteworthy nontumor effects in the Abstract.

Dr. Hook said there appeared to be two issues to be discussed and resolved, one having to do with the interpretative conclusions and the other having to do with the overall contents of the Technical Report. Dr. Swenberg said there appeared to be no disagreement on the carcinogenicity conclusions. Mr. Beliczky moved that the conclusions be accepted as written. Dr. Swenberg seconded the motion, and the conclusions were approved by seven affirmative votes with two abstentions (Dr. Holland and Dr. Scala).

The ensuing discussion concerned the amount of information to be released before final approval of the report by the Panel and what subsequent action should be proposed with respect to the full Technical Report including the hematologic data. There was some agreement that the conclusions be released with a brief introduction along with the data tables and text supporting the conclusions. The full Abstract would not be included because it had not been voted on. With regard to the final Technical Report, the prevailing view of Panel members was to review a revised report at a subsequent Peer Review meeting. Dr. Friess moved that the carcinogenesis results and interpretations be made available with the conclusions that were agreed upon and accepted by the Panel and that a full draft of the Technical Report on benzene be reviewed at an upcoming meeting. The motion was seconded and approved by seven affirmative votes with two abstentions (Dr. Holland and Dr. Scala).

PEER REVIEW PANEL (July 27, 1984)

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

National Toxicology Program Board of Scientific Counselors
Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)*
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

Curtis Harper, Ph.D. (Acting Chair)
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

James Swenberg, D.V.M., Ph.D.*
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D. (Principal Reviewer)
Board on Toxicology and Environmental Health Hazards
National Academy of Sciences
Washington, D.C.

Seymour L. Friess, Ph.D. (Principal Reviewer)
Arlington, Virginia

Thomas C. Jones, D.V.M.
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V. M., Ph.D.
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D.
Research Department
United Electrical, Radio and Machine Workers of America
New York, New York

Tom Slaga, Ph.D.*
Science Park, Research Division
University of Texas System Cancer Center
Smithville, Texas

Steven R. Tannenbaum, Ph.D.
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D.
Professor and Associate Director
College of Engineering
Cornell University
Ithaca, New York

John R. Van Ryzin, Ph.D. (Principal Reviewer)
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

* Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZENE (July 27, 1984 Meeting)

On July 27, 1984, the draft Technical Report on the toxicology and carcinogenesis studies of benzene received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The 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 draft Technical Report on the toxicology and carcinogenesis studies of benzene was initially evaluated by the Peer Review Panel on October 28, 1983. The interpretative conclusions on the carcinogenesis results were accepted by the Panel at that time; however, approval of the full Technical Report was deferred to allow for complete analyses of the hematologic data and inclusion of reportable findings into the report, and to allow for editorial tightening and incorporation of a number of suggested changes.

In the current review, Dr. Friess, a principal reviewer, again agreed with the conclusions. He noted that the conclusions relating to the hematologic findings, especially the dose-related lymphocytopenia and associated leucocytopenia, and suggested they be added to the conclusions on carcinogenicity. Dr. J. Huff, NTP, said this would be done.

As a second principal reviewer, Dr. Davis said some comment should be made on the use of corn oil as the vehicle in view of the possible cocarcinogenicity of corn oil. Dr. E. McConnell, NTP, pointed out that NTP is investigating the mechanism for these apparent effects (pancreatic lesions) associated with corn oil gavage (Boorman and Eustis, 1984). Dr. Huff said a manuscript (Haseman et al., 1985) had been accepted for publication regarding the incidence of neoplasms in untreated and corn oil gavage controls; where relevant, this reference would be cited in appropriate technical reports. In essence, he said that the historical control data on Fischer 344 (F344/N) rats and B6C3F$_1$ mice from the National Toxicology Program were examined to determine if animals receiving corn oil by gavage showed tumor incidences that differed from those in untreated control animals. Analyses of these data were adjusted for interlaboratory variability, time-related trends, and supplier effects. Two significant effects were found: male F344/N vehicle control rats receiving corn oil by gavage showed a significantly higher ($P<0.05$) incidence of pancreatic acinar cell adenomas and a significantly lower ($P<0.001$) incidence of leukemia (primarily mononuclear cell leukemia) than did the corresponding untreated controls. The increased incidences of pancreatic acinar cell adenomas observed in corn oil gavage male rats were associated with elevated body weights observed in these animals relative to those observed in untreated controls. Little difference in tumor incidence between corn oil gavage and untreated controls was observed in female F344/N rats and male and female B6C3F$_1$ mice. Dr. Davis said more mention should be given to the extensive epidemiologic studies on benzene.

As a third principal reviewer, Dr. Van Ryzin said the Technical Report was complete.

There was some discussion about the relevance of the gavage route versus other routes by which human exposure is more likely to occur, especially inhalation and dermal routes. Mr. Beliczky asked that a comment be included on skin absorption as an important route of entry. He referred to a study by the National Institute for Occupational Safety and Health which measured skin absorption in hairless mice. Dr. Tannenbaum stated that the route of administration can have a major influence on

the tumorigenicity of a chemical. Dr. Huff noted that Dr. C. Maltoni had demonstrated positive effects for benzene by both the inhalation and olive oil gavage exposure routes. Mr. Beliczky said that human risk assessments have been performed for benzene and should be referenced. Dr. Huff responded that additional references would be included on epidemiologic studies and situations of risk assessment.

Dr. Friess moved that the Technical Report on the toxicology and carcinogenesis studies of benzene be accepted with revisions as suggested. Mr. Beliczky seconded the motion, and the report was approved by nine affirmative votes. There was one absention (Dr. Kociba).

I. INTRODUCTION

STRUCTURE AND PROPERTIES

PRODUCTION, USE, AND OCCURRENCE

HUMAN EXPOSURE

EXPOSURE STANDARD

TOXICITY IN ANIMALS

METABOLISM AND EXCRETION

GENETIC TOXICOLOGY OF BENZENE

- Bacterial Systems
- Nonmammalian Eukaryotic Systems
- Mammalian Cells in Vitro
- Mammals in Vivo
- Cytogenetic Studies in Humans

FETOTOXICITY AND TERATOGENICITY

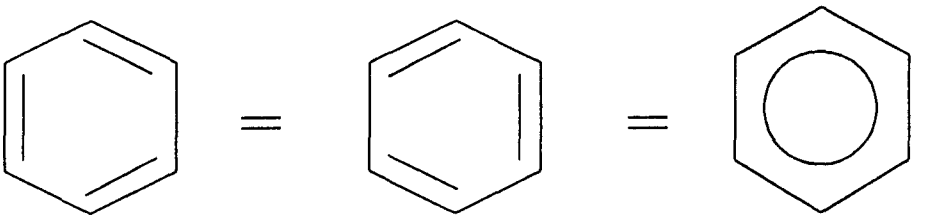
CARCINOGENICITY

CARCINOGENESIS STUDIES ON BENZENE METABOLITES

EFFECTS ON HUMANS

STUDY RATIONALE

I. INTRODUCTION



BENZENE

Benzol, Cyclohexatriene, Pyrobenzol

C_6H_6 MW = 78.11

C = 92.25% H = 7.75%

CAS No. 71-43-2

STRUCTURE AND PROPERTIES

The representation of the benzene molecule has evolved from the resonance ring structures described by Kekule in 1865 to the structure in which all six carbon-to-carbon bonds are identical (see above representations).

Benzene at room temperature is a highly flammable, colorless, transparent liquid having a boiling point of 80° C and a melting point of 5.5° C. Slightly soluble in water (1.8 g/liter), benzene is miscible with a variety of organic solvents and with oils. Benzene has a vapor pressure of 13 mm Hg, a flashpoint of −11° C, and a flammability limit in air of 1.5%-8.0%. It is generally available in three grades--refined, nitration, and industrial. The differences are based on the content of nonaromatics specified (less than 0.15% for refined) and on the distillation range (less than 1° C for refined and nitration grades and less than 2° C for industrial grade).

PRODUCTION, USE, AND OCCURRENCE

Benzene ranks 16th in production volume for chemicals produced in the United States, with approximately 9.9 billion pounds being produced in 1984, 9.1 billion pounds in 1983, and 7.8 billion pounds in 1982 (Chem. & Eng. News, 1985). This simplest aromatic chemical is used primarily as a raw material in the synthesis of styrene (polystyrene plastics and synthetic rubber), phenol (phenolic resins), cyclohexane (nylon), aniline, maleic anhydride (polyester resins), alkylbenzenes (detergents), chlorobenzenes, and other products used in the production of drugs, dyes, insecticides, and plastics (Purcell, 1978). Benzene, along with other light, high-octane aromatic hydrocarbons, such as toluene and xylenes, is a component of motor gasoline. Benzene is also used as a solvent, but for most applications, it has been replaced by less hazardous solvents.

Benzene has a long history of extensive use in industry, first as a volatile solvent and later as a starting material for the synthesis of other chemicals. An aromatic fraction containing benzene was known in the 18th century as a product of the distillation of coal (Purcell, 1978). Benzene, or bicarburet of hydrogen as it was then called, was first isolated in 1825 by Faraday, who obtained it from a liquid condensed by compressing oil gas. In 1833, Mitscherlich obtained bicarburet of hydrogen by distilling benzoic acid with lime and suggested the name "benzin" for the compound. Leibig objected and proposed "benzole." In 1845, benzene was found by Hoffman in light oil derived from coal tar. The commercial recovery of benzene from this source was developed and described by Mansfield in 1849. The synthesis of benzene by the polymerization of acetylene was first carried out by Berthelot in 1866. Discovery of benzene in coal gas after 1876 initiated the recovery of coal gas light oil as a source of benzene. Although petroleum was known to contain benzene, recovery of this material was not undertaken on a commercial scale until about 1941. Several years after the end of World War II, the demand for benzene by the rapidly expanding chemical

industry exceeded the total production by the coal carbonization industry. To help meet this deficit, benzene was produced in ever increasing amounts by the petroleum and petrochemical industries by the recovery from reformate and liquid byproducts of ethylene manufacture. Today, production from these sources far exceeds that from coal.

Benzene, the parent hydrocarbon of a series of aromatic compounds, should not be confused with the product benzin or benzine, a comparatively low boiling petroleum fraction consisting of a mixture of hydrocarbons, predominately aliphatic in type. The term "benzol" is used to describe commercial products that are largely benzene; the term is rarely seen in the United States but is still found in British publications. The pure compound is now called benzene, the name approved by the International Union of Pure and Applied Chemistry and adopted by industries and nomenclature experts.

Benzene recovered from both petroleum and coal sources is extracted from catalytic reformate made in oil refineries, from pyrolysis gasoline made in steam-cracking olefin plants, from light oils in coking coal, and from dealkylation of toluene (Chem. & Eng. News, 1980). The major derivatives of benzene are ethylbenzene (50%), cumene (15%), cyclohexane (15%), and aniline (5%). Primary end uses include polystyrene (25%), nylon (20%), other styrenic polymers (10%), and rubber (5%). As an antiknock chemical, benzene and benzene-enriched aromatics are added to gasoline as a replacement for alkyl lead compounds. The benzene content of European motor fuel is about 5% (CGOS, 1982); U.S. gasoline contains an average of 0.8% (IARC, 1982).

Benzene is apparently ubiquitous in the environment. The main source of benzene in the environment is from industrial processes. However, benzene is a natural constituent of crude oil (Brief et al., 1980). Early uses of benzene as a solvent regularly resulted in workplace air concentrations of 1,600-3,200 mg/m^3 (approximately 500-1,000 ppm) and above (IARC, 1982). In addition to the major source of benzene in the environment (industry), benzene is found in air, water, and sediments; soil and plants; food, beverages, and feed; tobacco and tobacco smoke; and pyrolysis products.

HUMAN EXPOSURE

Hunter (1978) chronicles the history of long-term benzene exposure; a few early facts are given here for historic interest. In the last years of the 19th century, the use of benzene as a rubber solvent led to small outbreaks of "purpura hemorrhagica" with a number of deaths from aplastic anemia. Selling (1916) was the first to associate benzene poisoning with leukopenia. Unfortunately, this association led to using benzene in the treatment of leukemia; benzene was given in gelatin capsules starting with 3 g per day and increasing to 5 g per day. The result was a gain in weight, shrinkage of the spleen, and great reduction of the white cell count. After some months of treatment, however, most patients developed multiple hemorrhages, especially from the fauces and gums; women experienced troublesome menorrhagia. With advancing anemia (loss of white and red blood cells), fever, and bleeding, these patients died of chronic poisoning. In most industrial countries, the use of benzene as a solvent increased after World War I. In 1922, Alice Hamilton began her efforts to reduce the hazards of benzene in American industry.

Workplace and environmental exposure to benzene is widespread. As many as 2 million workers may be exposed (NIOSH, 1977; Brief et al., 1980). Nonoccupational exposure to benzene results primarily from environmental contamination, the chief sources being automobile and factory emissions and cigarette smoke. Benzene intake by urban residents in the United States is approximately 850 µg per day (NRC, 1980). Benzene is present in cigarette smoke at concentrations of 47-64 ppm (Lauwerys, 1979). Dietary intake may be as high as 250 µg per day (NRC, 1980). Benzene has been identified in bottled artesian water (Dowty et al., 1975) and in boiled beef and canned beef stew (Chang and Peterson, 1977).

Two recent studies have shown considerable benzene absorption via skin. Susten et al. (1985), using hairless mice, calculated that 20%-

40% of the total benzene dose received by humans in tire-building operations could be absorbed dermally. Blank and McAuliffe (1985) calculated that an adult working in ambient air containing 10 ppm benzene would absorb 7.5 µl per hour from inhalation and 1.5 µl per hour from whole body (2 m^2) exposure. They also calculated that 100 cm^2 glabrous skin in contact with gasoline containing 5% benzene would absorb 7.0 µl per hour. These results are not too different from those decided by Susten et al. (1985) using mouse skin.

EXPOSURE STANDARD

Adopted in 1971, the present Occupational Safety and Health Administration (OSHA) standard for benzene is an 8-hour time-weighted average (TWA) of 10 ppm with a ceiling limit of 25 ppm and a maximum peak concentration of 50 ppm for a 10-minute period (Fed. Reg., 1985). The standard apparently was based on concern about the development of aplastic anemia and depression of various cellular elements in the blood, but not on concern about the development of cancer. In May 1977, OSHA issued an Emergency Temporary Standard that reduced exposures to benzene to 1 ppm and included other provisions. In February 1978, OSHA promulgated a new permanent standard for occupational exposure to benzene based on evidence that there was a causal connection between benzene exposure and leukemia. This standard limited employee exposure to 1 ppm as an 8-hour TWA, the level then estimated to be the lowest feasible. The standard included a ceiling limit of 5 ppm for any 15-minute period during an 8-hour day, limits on eye and skin contact with benzene, and industrial hygiene and medical surveillance provisions.

The United States Court of Appeals for the Fifth Circuit vacated the standard in 1978 and the Supreme Court affirmed that judgment in 1980. The Supreme Court held that OSHA's prior approach (reducing exposures to the lowest feasible level when there was strong qualitative evidence of carcinogenicity) was insufficient.

In December 1985, OSHA issued a newly proposed rule and notice of hearing on occupational exposure to benzene (Fed. Reg., 1985). In this announcement, OSHA "proposes to reduce the existing benzene permissible exposure limit of 10 parts benzene per million parts of air (10 ppm) to an eight (8)-hour time-weighted average of 1 ppm to reduce substantially a significant health risk." The current 10-ppm exposure limit in the United States corresponds to that in most other industrialized countries, except for Sweden (5 ppm) and the USSR (5 mg/m^3 approximately equivalent to 2 ppm) (Holmberg and Lundberg, 1985).

TOXICITY IN ANIMALS

The Proceedings of the International Collegium Ramazzini Conference on Benzene held in New York, New York, on November 3-4, 1983, have been published (Am. J. Ind. Med., 1985; Mehlman, 1985).

The following oral LD_{50} values have been reported for benzene: 0.93 g/kg for Sprague-Dawley rats (Cornish and Ryan, 1965), 3.8 ml/kg for young adult male Sprague-Dawley rats (Kimura et al., 1971), and 5.6 g/kg for male Wistar rats (Wolf et al., 1956). The LC_{50} value for a 7-hour exposure is 10,000 ppm for mice (Svirbely et al., 1943).

Depression of bone marrow function, resulting in leukopenia, was observed in rodents exposed to benzene: Sprague-Dawley rats (44 ppm, 5 hours per day, 4 days per week for 5 weeks); AKR/J mice (300 ppm, 6 hours per day for 28 days); and male CD-1 mice (103 ppm, 6 hours per day, 5 days per week, for 26 weeks). Similar results were also obtained in Wistar rats administered benzene orally (1 mg/kg for 14 days) and F344 rats administered benzene by subcutaneous injection (1 ml/kg per day for 10 days) (Gerarde, 1956; Deichmann et al., 1963; Irons et al., 1979; Green et al., 1981). Pretreatment of rats with Aroclor 1254® resulted in decreased polyphenolic metabolites located in bone marrow and provided protection against benzene-induced lymphocytopenia (Greenlee et al., 1981). Relative spleen weights were reduced in DDF_1 mice administered benzene by inhalation (4,680 ppm, 8 hours per day for 3 days), and involution of the spleen occurred in Wistar rats administered 1 mg/kg by gavage for 14 days (Uyeki et al., 1977; Gerarde, 1956).

The hematotoxicity of benzene has been studied extensively, and a number of review articles have been published (IARC, 1982; Laskin and Goldstein, 1977; Snyder and Kocsis, 1975). The large literature on the effects of benzene on the hematopoietic system is not discussed in this report.

METABOLISM AND EXCRETION

After monosubstitution of benzene has occurred, three disubstitution positions are chemically possible: 1,2- (*ortho*-); 1,3- (*meta*-); or 1,4- (*para*-). Electron-withdrawing groups promote meta-substitutions and electron donating groups favor *ortho*- and *para*- substitutions. Since most benzene metabolites are hydroxyl additions, the *ortho*-/*para*- positions predominate (Purcell, 1978). Following metabolic formation of phenol (C_6H_5OH), further metabolism leads to both catechol (pyrocatechol; *ortho*-dihydroxybenzene) and hydroquinone (*para*-dihydroxybenzene). The third possible form, *meta*-dihydroxybenzene (resorcinol), probably does not occur. As described by Irons and Pfeifer (1982), the primary oxidation of benzene occurs via the cytochrome P-450-dependent monooxygenase system, resulting in biologically reactive intermediates (Figure 1). As generally agreed, benzene per se does not represent the principal structural moiety causing the identified toxic effects on the bone marrow or lymphoid system (Irons and Pfeifer, 1982; Bolcsak and Nerland, 1983). The metabolism and elimination of benzene in humans appear to be similar to those in rats and mice; the amounts of various metabolites, the extent of metabolism, and the nature of the phenol conjugates depend on the species, strain, and the route of administration (Rusch et al., 1977).

The National Institute of Environmental Health Sciences is conducting studies of the comparative metabolism and disposition of benzene and its metabolites in selected tissues in F344 rats and $B6C3F_1$ mice by the oral and inhalation routes (Sabourin et al., 1986). In both species, metabolism of benzene is nonlinear at all doses above 50 mg/kg. During 6-hour inhalation exposures, metabolism is exponentially related to vapor concentration. One-half maximal saturation occurs at 280 ppm in rats and at 115 ppm in mice. Animals are exposed to ^{3}H-benzene at 0.5-300 mg/kg per day (oral) or 1.0-300 ppm for 6 hours per day (inhalation) for 5 days. Following the final exposure, animals will be killed at multiple time points and benzene and its metabolites quantitated in urine, blood, feces, liver, lung, bone marrow, and Zymbal gland. Metabolites in oral cavity, stomach, skin around the mouth, and skin on the back will be analyzed only at the low and high doses. Metabolites to be analyzed by high-performance liquid chromatography include benzene, trihydroxybenzene, hydroquinone, catechol, phenol, muconic acid, and water soluble conjugates. To date, exposure of F344 rats and $B6C3F_1$ mice to ^{3}H-benzene at 0.5, 5, 15, 50, 150, and 300 mg/kg per day by the oral route has been completed, and tissue samples are currently being analyzed for both water-soluble and unconjugated metabolites. To determine the actual exposure of the animal to a given dose of benzene requires that the amount of uptake be known. Therefore, the gastrointestinal and pulmonary uptake of ^{14}C-benzene is being investigated. Gastrointestinal uptake studies indicate nearly 100% uptake of orally administered benzene by the gastrointestinal tract in all three animal strains. At 300 mg/kg, approximately 60% of the administered benzene is exhaled and the remainder is excreted in the urine. However, at a dose of 0.5 mg/kg, almost all of the ^{14}C-benzene equivalents are excreted in the urine.

GENETIC TOXICOLOGY OF BENZENE

A summary of the genetic toxicology of benzene is shown in Table 2. Recent findings on the genetic toxicology of benzene and other solvents (toluene, xylenes, phenols) have been summarized by Dean (1985).

Bacterial Systems

Many studies have shown that benzene is not mutagenic in bacteria. Eight strains of Salmonella have been used, and rat liver S9 has been prepared from uninduced animals and from animals induced with 3-methylcholanthrene, phenobarbital, or Aroclor 1254 (Simmon et al., 1977;

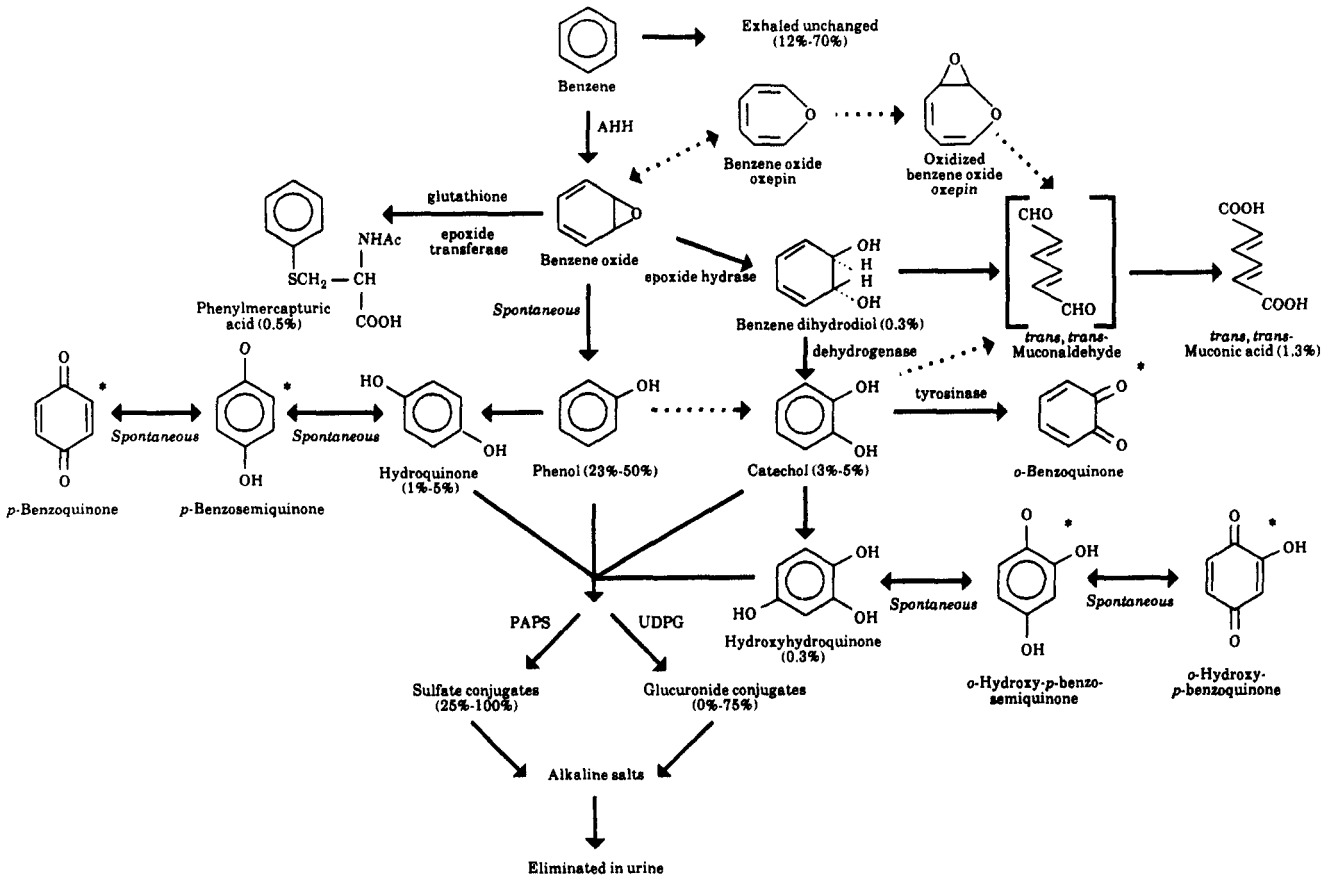


FIGURE 1. PATHWAYS OF BENZENE METABOLISM AND EXCRETION

Adapted from Parke and Williams, 1953; Laskin and Goldstein, 1977; Goldstein et al., 1982; Irons and Pfeifer, 1982; Pfeifer and Irons, 1983; Erexson et al., 1985; Sawahata et al., 1985. Values in parentheses are percentages of metabolic products detected in urine of animals (rabbits, rats, mice, dogs) or humans. Asterisks denote putative or demonstrated alkylating activity toward intracellular nucleophiles AHH = aryl hydrocarbon hydroxylase; UDPG = uridine diphosphate glucuronyl transferase; PAPS = 3'-phospho-adenosine-5'-phosphosulfate. Dashed lines indicate putative pathways. *trans, trans*-Muconaldehyde is a postulated intermediate.

TABLE 2. SUMMARY OF THE GENETIC TOXICOLOGY OF BENZENE

Test System	Endpoint	Result	References
Bacterial Systems			
Salmonella typhimurium	Gene mutation	–	Lyon, 1975
		–	Cotruvo et al., 1977
		–	Simmon et al., 1977
		–	Shahin and Fournier, 1978
		–	Kaden et al., 1979
		–	Bartsch et al., 1980
		–	Florin et al., 1980
		–	Ho et al., 1981
		–	Hermann, 1981
Bacillus subtilis		–	Tanooka, 1977
B. subtilis	DNA damage	+	McCarroll et al., 1981a
Escherichia coli		+	McCarroll et al., 1981b
E. coli		–	Rosenkranz and Leifer, 1980
Nonmammalian Eukaryotes			
Saccharomyces cerevisiae	Gene mutation	–	Egilsson et al., 1979
Tradescantia		+	Schairer et al., 1978
		+	Schairer and Sautkulis, 1982
Drosophila melanogaster		–	Nylander et al., 1978
		–	Kale and Baum, 1983
Mammalian Cells (in vitro)			
Mouse lymphoma	Gene mutation	–	Lebowitz et al., 1979
Human leukocytes	Chromosomal aberrations	+	Koizumi et al., 1974
Human lymphocytes	Chromosomal aberrations	+	Morimoto, 1974
		–	Gerner-Smidt and Friedrich, 1978
	Sister-chromatid exchanges	–	Gerner-Smidt and Friedrich, 1978
		–	Morimoto and Wolff, 1980
		+	Morimoto, 1983
		+	Morimoto et al., 1983
Chinese hamster ovary cells	Chromosomal aberrations	–	NTP (Appendix G)
Mammals (in vivo)			
Mice	Micronuclei	+	Diaz et al., 1980
		+	Hite et al., 1980
		+	Meyne and Legator, 1980
		+	Siou et al.,1981
		+	Tunek et al., 1982
		+	NTP (Appendix G)
	Chromosomal aberrations	+	Meyne and Legator, 1980
		+	Tice et al., 1980
		+	Siou et al., 1981
		+	Tice et al., 1982

TABLE 2. SUMMARY OF THE GENETIC TOXICOLOGY OF BENZENE (Continued)

Test System	Endpoint	Result	References
Mammals (in vivo)			
Mice (Continued)			
	Sister-chromatid exchanges	+	Tice et al., 1980
		+	Tice et al., 1982
	Sperm morphology	+	Topham, 1980
Rats	Micronuclei	+	Lyon, 1975
	Chromosomal aberrations	+	Lyon, 1975
		+	Dean, 1969
		+	Anderson and Richardson, 1981
	Sperm morphology	–	Lyon, 1975
Hamsters	Micronuclei	–	Siou et al., 1981
	Chromosomal aberrations	–	Siou et al., 1981
Rabbits	Chromosomal aberrations	+	Kissling and Speck, 1971
Humans	Chromosomal aberrations	+	Reviewed by IARC, 1982

Cotruvo et al., 1977; Shahin and Fournier, 1978: Florin et al., 1980; Ho et al., 1981; Hermann, 1981). Although all of these studies used the standard plate-incorporation assay described by Ames et al. (1975), negative results were obtained in a host-mediated assay that consisted of strain TA1950 injected intraperitoneally into Swiss albino mice; the mice then received two subcutaneous 0.1-ml injections of benzene at 1-hour intervals (Lyon, 1975). Bartsch et al. (1980) exposed strains TA98 and TA100 in inverted Petri dishes at concentrations less than or equal to 20% benzene (v/v) in air in a 10-liter desiccator for 4 or 12 hours at 37° C. The results were negative in the presence or absence of Aroclor-induced rat liver S9. Although all of these studies were reverse-mutation assays at a histidine gene in Salmonella, a forward-mutation assay in Salmonella for resistance to 8-azaguanine also failed to detect any mutagenic activity of benzene (Kaden et al., 1979). Benzene not only failed to revert a variety of strains of Salmonella but also did not revert a histidine auxotroph of *Bacillus subtilis* (Tanooka, 1977). Although McCarroll et al. (1981a,b) reported that benzene caused growth inhibition by producing DNA damage in *B. subtilis* and *Escherichia coli*, Rosenkranz and Leifer (1980) found that benzene was negative in the *E. coli* pol A test.

Nonmammalian Eukaryotic Systems

Benzene failed to induce petites in yeast (Egilsson et al., 1979) and was negative for both somatic mutation (Nylander et al., 1978) and germ cell mutation (sex-linked recessive lethal) in Drosophila (Kale and Baum, 1983). However, exposure of vascular plant *Tradescantia* resulted in mutations (Schairer et al., 1978; Schairer and Sautkulis, 1982). Thus, it appears that this higher plant may be capable of metabolizing benzene to mutagenic metabolites.

Mammalian Cells in Vitro

Benzene was not mutagenic in the mouse lymphoma forward-mutation assay in L5178Y/TK$^{+/-}$ cells (Lebowitz et al., 1979). However, the genotoxic effects of benzene have been studied in cultured human cells. Koizumi et al. (1974) showed that benzene inhibited DNA synthesis in HeLa cells and in human leukocytes in vitro. The authors also found that benzene induced chromosome breaks and gaps in cultured human leukocytes, but high doses (1.1 and 2.2 $\times$ 10^{-3} M) and long exposure times (72 hours) were

required to produce the chromosomal abnormalities. Morimoto (1974) reported that treatment of cultured human lymphocytes with benzene at high doses (2×10^{-4} to 3×10^{-3} M) for long exposure times (53 hours) caused chromosomal abnormalities, including acentric fragments, breaks, and gaps. These observations were not confirmed by Gerner-Smidt and Friedrich (1978), who treated cultured human lymphocytes with benzene (2.1×10^{-2} M) for 72 hours and found no increase in either chromosomal aberrations or in sister-chromatid exchanges (SCE's). Likewise, Morimoto and Wolff (1980) found that benzene (5×10^{-3} M for 72 hours) did not induce SCE's in cultured human lymphocytes; these authors did find, however, that two major metabolites, catechol and hydroquinone, induced SCE's at low concentrations (3 and 9×10^{-5} M, respectively). None of these studies in cultured human cells incorporated exogenous metabolic activation. Benzene did not induce SCE's or chromosomal aberrations in Chinese hamster ovary (CHO) cells in the presence or absence of Aroclor-induced rat liver S9 (Appendix G). Morimoto (1983) and Morimoto et al. (1983) reported that benzene induced SCE's in vitro, but high doses of benzene (5 mM) and of S9 (10%-20%) were required.

Mammals in Vivo

Although benzene has given mixed results for the induction of SCE's and for chromosomal aberrations in vitro, it is one of the few compounds that has been tested extensively for a variety of cytogenetic effects in vivo. There are now a dozen studies that show that benzene causes cytogenetic damage in rodents in vivo; of these, eight are in mice (Diaz et al., 1980; Hite et al., 1980; Meyne and Legator, 1980; Tice et al., 1980; Siou et al., 1981; Tice et al., 1982; Tunek et al., 1982; NTP, Appendix G); three are in rats (Dean, 1969; Lyon, 1975; Anderson and Richardson, 1981); and one is in rabbits (Kissling and Speck, 1971). However, benzene failed to induce cytogenetic damage in hamsters (Siou et al., 1981).

Micronuclei. Micronuclei are chromosomes or small fragments of chromosomes that are not incorporated into daughter nuclei during cell division. They may be induced by agents that break chromosomes (clastogens) or that affect the spindle apparatus. The ability of benzene to induce micronuclei in the bone marrow polychromatic erythrocytes of mice has been confirmed by five independent studies in five strains of mice. Diaz et al. (1980) and Tunek et al. (1982) administered benzene subcutaneously to male mice (the F_1 from the cross CSW $\times$ Cs No. 1 or outbred NMRI) and observed a dose-dependent increase in micronuclei. Benzene was administered by gavage to male and female mice in the following three studies. Hite et al. (1980) found that benzene induced similar dose-dependent increases in micronuclei in both sexes of Charles River (CD-1) mice. Meyne and Legator (1980) and Siou et al. (1981), who used Swiss (CD-1) and Swiss Lane Petter mice, respectively, also found that benzene induced micronuclei in both sexes, but with greater dose-dependent increases in micronuclei in males than in females. Siou et al. (1981) showed that castration of males reduced their sensitivity for micronuclei formation below that of the females. Meyne and Legator (1980) found that intraperitoneal injections of benzene produced a dose-dependent increase in micronuclei in males and yet caused no increase in micronuclei in females. The NTP (Appendix G) found that benzene administered by gavage induced micronuclei in male and female $B6C3F_1$ mice; males were more sensitive than females (Choy et al., 1985). In male Long-Evans rats, intraperitoneal injections of benzene induced a dose-dependent increase in micronuclei, and the doses were similar to those that induced micronuclei in mice (Lyon, 1975). Although benzene induced micronuclei in mice and rats, Siou et al. (1981) did not find an increase in micronuclei in hamsters that received benzene by gavage.

Chromosomal Aberrations. Meyne and Legator (1980) reported that exposure of Swiss (CD-1) mice to benzene by gavage or intraperitoneal injection increased the frequency of chromosomal aberrations and that males were more sensitive than females. However, Tice et al. (1980) found that exposure of DBA/2 mice to benzene by inhalation caused an increase in chromosomal aberrations only when the animals had been pretreated with phenobarbital. The authors also showed that the combination of benzene and phenobarbital inhibited cellular proliferation in

the bone marrow; once again, males were more sensitive to this inhibition than were females. Subsequent studies (Tice et al., 1982) showed that the combination of benzene and phenobarbital enhanced the frequency of chromosomal aberrations in males more than in females. The aberrations were all of the chromatid-type, not of chromosome-type, and there were no increases in chromosomal rearrangements of any kind. Siou et al. (1981) confirmed the observations of Meyne and Legator (1980) by administering benzene by gavage to Swiss Lane Petter mice: chromosome gaps were enhanced in both sexes, and males were more sensitive than females.

Three reports show that benzene induces chromosomal aberrations in rats. Lyon (1975) injected benzene intraperitoneally into male Long-Evans rats and found a significant increase in chromosomal aberrations in bone marrow cells, including achromatic lesions, chromatid and chromosome deletions, and double minutes (small supernumerary chromosomal fragments). Dean (1969) reported that benzene injected intraperitoneally into Carworth CF_1 rats increased the number of chromatid gaps and chromosome fragments in bone marrow cells from both sexes. Anderson and Richardson (1981) examined the ability of benzene to induce chromosomal aberrations in the bone marrow cells of Wistar-derived male Alderly Park rats. Exposure by inhalation or injection increased the frequency of chromosomal aberrations. No dose response was observed, and a single exposure was as effective as multiple doses. A significant increase in chromosomal aberrations, mostly gaps and breaks, was found in rabbits injected subcutaneously with benzene (Kissling and Speck, 1971).

Although benzene induces chromosomal aberrations in mice, rats, and rabbits, a similar effect has not been seen in Chinese hamsters. Siou et al. (1981) administered benzene by gavage to Chinese hamsters and reported no increase in chromosomal aberrations. This result suggests that hamsters' sensitivity to benzene is different from that of other rodents.

Sister Chromatid Exchanges. The ability of benzene to induce SCE's in mice was reported by Tice et al. (1980, 1982): inhaled benzene enhanced the frequency of SCE's in male and female DBA/2 mice, but more so in males. Three-month-old mice were more sensitive than were 10-month-old mice. The authors also compared effects resulting from two different routes of exposure and found that inhalation of 120 ppm of benzene for 4 hours equaled the effect of an intraperitoneal injection of 1 mmole/kg. Although additional experiments are still in progress, the authors have tentatively concluded that a greater increase in SCE's results from inhaled benzene than from injected benzene. In contrast to their other findings, these authors also found that treatment with phenobarbital before inhalation of benzene enhanced SCE's in male and female mice but more so in females. Inhaled benzene also caused a greater increase in SCE's in DBA/2 mice than in C57BL/6 mice. These two strains are isogenic and vary in that DBA/2 mice have no inducible aryl hydrocarbon hydroxylase (AHH) activity, whereas the C57BL/6 strain does.

Other Endpoints. An additional endpoint, sperm-head abnormalities, has been studied by Topham (1980), who showed that hybrid mice (CBA × BALB/c) given intraperitoneal injections of benzene exhibited small but reproducible and significant increases in sperm-head abnormalities. Earlier, Lyon (1975) found that intraperitoneal injections of benzene in Long-Evans rats at 0.5 ml/kg (one-fifth the LD_{50} value) did not increase the frequency of dominant lethals.

Cytogenetic Studies in Humans

Benzene is one of the few agents whose cytogenetic effects have been studied in humans. The populations studied can be divided into two general groups: (1) people with a current or past history of benzene-associated blood dyscrasias and (2) workers with current or past exposure to benzene but with no apparent clinical signs of blood dyscrasias. In many of the 23 studies (IARC, 1982), significant increases in chromosomal aberrations were observed, which in some cases persisted for years after exposure ceased. Most of these studies involved small numbers of humans exposed to benzene and did not present detailed information about the concentration and length of exposure. Although the data do not

support a clear association between exposure to benzene and persistent chromosomal aberrations, the data do indicate an association between benzene-associated hemopathies and chromosomal aberrations.

In summary, these studies show that benzene is clearly a clastogen and that benzene causes other chromosomal changes. The data further suggest that benzene is not a gene mutagen, an agent that causes a molecular change in a gene as opposed to a chromosome. In addition, benzene must be metabolized in vivo to cause chromosomal changes, suggesting that metabolites of benzene are responsible for any observed cytogenetic changes. In general, male rodents are more sensitive than females to the genotoxic effects of benzene, and the route of administration influences the ability of benzene to induce chromosomal damage. Cytogenetic damage also has been observed in humans who have developed benzene-associated hemopathies, especially leukemia.

FETOTOXICITY AND TERATOGENICITY

Cleft palate, agnathia, and micronathia were associated with a single subcutaneous injection of 3 ml/kg to CF-1 mice on day 13 of gestation (Watanabe and Yoshida, 1970). This study was considered to be less than adequate, however, because no controls were used. Delayed ossification of sternebrae was observed in the offspring of Sprague-Dawley rats exposed to air containing 300 or 2,200 ppm benzene for 6 hours per day on days 6-15 of gestation (Green et al., 1978). Significantly increased incidences of missing sternebrae were observed in the female offspring after exposures of the mothers at 2,200 ppm. Delayed ossification was also found in the fetuses of Sprague-Dawley rats exposed to air containing 50 or 500 ppm benzene, 7 hours per day on day 6-15 of gestation. The mean number of caudals (vertebrae) in the fetuses of the rats that were exposed was significantly less than that in the fetuses of controls (Kuna and Kapp, 1981). Skeletal retardation and abnormalities (but not malformations) were observed in the offspring of CFY rats exposed to air containing 313 ppm benzene, 24 hours per day on days 9-14 of gestation (Hudak and Ungvary, 1978).

No teratogenic effects were observed in offspring following 6-hour daily exposure of pregnant Sprague-Dawley rats to benzene vapor at 0, 1, 10, 40, or 100 ppm on days 6-15 of gestation (API, 1982). A slight fetotoxic effect (reduced mean fetal body weights) was reported for both sexes of offspring of the mothers that were exposed to benzene at 100 ppm. The available data on teratologic studies have been summarized (Schwetz, 1983; Mehlman et al., 1981). Schwetz (1983) concluded that benzene has not been found to be teratogenic in laboratory animals exposed during the critical period of development of the embryo or fetus. After review of the teratogenic studies, the author stated that exposure to benzene at levels that do not cause other forms of toxicity would not be expected to cause adverse developmental effects. Davis (1986) reviewed the literature on the reproductive risks of benzene and concluded that more animal and epidemiologic studies are needed before more definitive conclusions can be made.

CARCINOGENICITY

Bone marrow hyperplasia, thymic lymphoma (6/40), plasmacytoma (1/40), and leukemia (1/40) were reported in C57BL/6J mice exposed to air containing 300 ppm benzene for 6 hours per day, 5 days per week, for 488 days as compared with an incidence of 2/40 lymphoma (nonthymic) in the controls (Snyder et al., 1980). (Only thymuses appearing to be abnormal at necropsy were examined microscopically.) Myelogenous leukemia occurred in 2/40 CD-1 mice exposed to air containing 300 ppm benzene for 6 hours per day, 5 days per week, for life, but these cannot be clearly related to chemical exposure (Goldstein et al., 1982). The reported findings from these studies do not allow any positive associations because of the marginal increases together with the small numbers of animals used.

Zymbal gland carcinomas were observed in 8/32 (25%) female Sprague-Dawley rats administered 250 mg/kg benzene in olive oil by gavage four or five times per week for 52 weeks, followed by 92 weeks of observation (Maltoni and Scarnato, 1979; Maltoni et al., 1982c, 1983). Squamous cell carcinomas of the oral cavity were associated with the administration by gavage of 500

mg/kg benzene to Sprague-Dawley rats once a day for 104 weeks (Maltoni et al., 1982a). Increased incidences of hepatocarcinomas were found in Sprague-Dawley rats exposed to air containing 200-300 ppm benzene, 4-7 hours per day for up to 104 weeks (Maltoni et al., 1982b). IARC (1982) summarized the 15 available studies on benzene (1932-1981), and Van Raalte and Grasso (1982) reviewed the available carcinogenesis data on benzene through mid-1982.

Cronkite et al. (1985) reported that exposure of male and female C57BL/6 BNL mice to benzene vapor at or above 100 ppm for 10 exposures (6 hours per day, 5 days per week) reduced bone marrow cellularity and the number of pluripotent stem cells. Exposure at 300 ppm for 2, 4, 8, and 16 weeks showed a time-related decrease in stem cell levels and extended recovery periods. Cronkite et al. (1984, 1985) showed that female mice exposed at 300 ppm (6 hours per day, 5 days per week for 16 weeks after which exposure was stoppped) exhibited increased incidences of leukemia (8/88 versus 20/89) largely due to thymic lymphomata (1/88 versus 10/89). In addition, Zymbal gland neoplasia (1/88 versus 16/89) and ovarian tumors (0/88 versus 8/89) were increased. These authors suggest that continuous exposure either suppresses the incidence of lymphoma in mice or shortens the life span, so lymphomas cannot be observed. Thus, shorter term or fractionated exposures of laboratory animals may result in higher incidences of neoplasia than longer term (2-year) continuous exposures.

Maltoni et al. (1985) summarized a series of long-term gavage and inhalation studies conducted or ongoing at the Bologna Institute of Oncology, Italy. These authors reported an association of benzene exposure with Zymbal gland carcinomas, oral and nasal cavity carcinomas, skin carcinomas, acanthomas, forestomach carcinomas, mammary malignant tumors, hepatomas, liver angiosarcomas, hemolymphoreticular neoplasms, and pulmonary tumors. Details about these experiments are given in Maltoni et al. (1985) as well as in numerous other publications on these data from this laboratory.

CARCINOGENESIS STUDIES ON BENZENE METABOLITES

Phenol (CAS No. 108-92-2): Carcinogenesis studies of phenol were conducted by providing drinking water containing 0, 2,500, or 5,000 ppm to F344 rats and to B6C3F$_1$ mice for 103 weeks (NCI, 1980; Huff, 1983). An increased incidence of neoplasms was detected in low dose male rats (leukemia--18/50, 30/50 [$P<0.05$], 25/50; pheochromocytoma of the adrenal glands--13/50, 22/50 [$P<0.05$], 9/50; and C-cell carcinoma of the thyroid gland--0/50, 5/49 [$P<0.05$], 1/50). No chemical-related neoplasms were observed in female rats or in male and female mice. Salaman and Glendenning (1957), Boutwell and Bosch (1959), Wynder and Hoffmann (1961), Van Duuren et al. (1968), and Van Duuren and Goldschmidt (1976) have shown that phenol in acetone or in benzene promotes skin cancer in mice pretreated with 7,12-dimethylbenz(a)anthracene (DMBA) or 3,4-benzo(a)pyrene (B[a]P). Phenol did not exhibit any cocarcinogenic effects when given with B[a]P (Van Duuren et al., 1973; Van Duuren and Goldschmidt, 1976).

Catechol (CAS No. 120-80-9): In 1951, Lehman et al. reported a study in which groups of 12-18 rats were exposed to 0.0625%-1.0% catechol in the diet for 2 years. The only response recorded was "beginning hepatic cell hyperplasia" in the 0.25% group. In a short-term skin tumor-promoting study, 30 female Sutter mice received 0.3 ml DMBA in benzene and, beginning 1 week later for 15 weeks, a single drop of 15% catechol in benzene. No promoter activity was observed (Boutwell and Bosch, 1959). Van Duuren and Goldschmidt (1976) applied 150 µg B[a]P topically to the dorsal skin of 50 female Swiss mice and 14 days later applied 2 mg catechol in 0.1 ml acetone three times per week until day 448. No tumor-promoting activity was found. Hecht et al. (1975) applied 75 µg DMBA in 0.1 ml acetone to groups of 30 female Swiss mice one time only, followed 10 days later with 0.1 ml of a 1% catechol/acetone (1 mg of catechol) solution five times per week for 67 weeks. In these studies, catechol was inactive as a tumor promoter. Van Duuren el al. (1973) and Van Duuren and

Goldschmidt (1976) applied 2 mg catechol with and without 5 μg B[a]P in 0.1 ml acetone to groups of 50 female Swiss mice three times per week for 368 days. Of the mice dosed with catechol and B[a]P in combination, 36 had skin papillomas (2.5 per mouse) and 31 had skin squamous cell carcinomas. In the group receiving only catechol, one mouse had a skin papilloma and one had a squamous cell papilloma. Thirteen mice receiving B[a]P had skin papillomas (1.1 per mouse), and 10 had squamous cell carcinomas. In these experiments, catechol increased the carcinogenic activity of B[a]P. Subsequently, Hecht et al. (1981) tested a subfraction of cigarette smoke condensate containing 97% catechol on groups of 30 female Swiss mice. A 0.25% catechol-acetone solution (0.1 ml) alone or with 0.003% B[a]P was applied five times per week for 52 weeks (this dose was about one-sixth the dose used by Van Duuren and Goldschmidt, 1976). The combination caused increased incidences of neoplasms per mouse (1.4 versus 0.1) and greater percentages of mice with total skin tumors (73% versus 14%) and squamous cell carcinomas (64% versus 11%). This study confirms that catechol possesses cocarcinogenic effects. Boyland et al. (1964) implanted 10-mg cholesterol pellets alone or containing 20% catechol into the urinary bladders of mice. Of the 19 mice that received the combination pellet and survived the 25-week experiment, 1 (5.3%) had a papilloma and 3 (15.8%) had carcinomas. Of 77 mice with cholesterol pellets, 4 (5%) had adenomas or papillomas and 5 (6.5%) had carcinomas. A marginal decrease ($P=0.03$) was observed for the catechol group (4/19, 21.1%, versus 9/77, 11.7%).

Hydroquinone (CAS No. 123-31-9): Lehman et al. (1951) fed hydroquinone at 0.125%-2.0% in the diet to groups of 12-18 rats for 2 years. The authors reported a "suggestion" of gastrointestinal ulceration and renal tumors in the 2% group. Carlson and Brewer (1953) offered diets containing 0%-0.5% or 0%-1.0% (four concentrations) with 0.1% citric acid to groups of 10-23 male and female rats for 103 weeks. No adverse hematologic or histopathologic effects were recorded. Roe and Salaman (1955) applied 0.3 ml of a 6.7% hydroquinone-acetone solution (20 mg dose) to the backs of male "S"-strain mice. Three weeks later, croton oil (0.3 ml of a 0.5% acetone solution) was applied dermally once a week for 18 weeks. One of the 22 survivors had a skin papilloma. Hydroquinone was inactive as an initiator of skin carcinogenesis.

Using experimental conditions similar to those described above for catechol, Boutwell and Bosch (1959) and Van Duuren and Goldschmidt (1976) reported that hydroquinone had no promoter activity with DMBA or B[a]P. Boyland et al. (1964) tested hydroquinone as 20% in 10-mg cholesterol pellets implanted in the urinary bladder of mice. Six of the 19 survivors (32%) at week 25 had bladder carcinomas, whereas four benign and five malignant neoplasms were found in 77 cholesterol controls (11.7%). In this study, hydroquinone was considered carcinogenic.

In cocarcinogenesis studies, Van Duuren and Goldschmidt (1976) applied hydroquinone in doses of 5 mg with and without 5 μg B[a]P in acetone (see details under catechol). Hydroquinone with B[a]P induced fewer skin neoplasms than B[a]P alone (7 mice with 11 papillomas and 3 with squamous cell carcinomas versus 14 mice with 16 papillomas and 10 with squamous cell carcinomas).

The National Toxicology Program has conducted 2-year carcinogenesis studies of hydroquinone in male and female F344/N rats and $B6C3F_1$ mice. Hydroquinone was given in water by gavage at doses of 0, 25, or 50 mg/kg for rats and 0, 50, or 100 mg/kg for mice. The experiments began in August 1982, the exposure phase was completed in August/September 1984, and the initial histopathology diagnoses are being evaluated.

p-Quinone (CAS No. 106-51-4: Three carcinogenesis studies have been reported (IARC, 1977). In 1940, Takizawa painted the skin of mice every 1 or 2 days for about 200 days with 0% (benzene), 0.1%, or 1.25% *p*-benzoquinone in benzene. Of 46 controls, 1 had a skin papilloma and 2 had adenocarcinomas of the lung. Among the 41 mice at 0.1%, 6 had skin papillomas, 2 had skin carcinomas, and 10 developed lung adenocarcinomas. In the 0.25% group (44 mice), 3 had skin papillomas, 1 had a skin carcinoma, and 5 had lung adenocarcinomas. In a series of three inhalation experiments, Kishizawa (1954, 1955, 1956) exposed groups of 25 mice to air

containing 0 or 5 mg *p*-quinone, once per day, six times per week. The numbers of mice with neoplasms of the lung were not different between control and dosed groups. Umeda (1957) conducted studies in 24 rats by subcutaneously injecting 0.5 ml of propylene glycol with *p*-quinone once per week for 394 days (concentrations were 1% from days 1 to 53, 0.2% from days 54 to 173, and 0.4% from days 173 to 394). Of 17 surviving rats receiving 32 injections (81 mg *p*-quinone and 16.5 ml propylene glycol), 2 developed injection-site fibrosarcomas.

EFFECTS ON HUMANS

Humans are susceptible to benzene myelotoxicity as shown by the high incidence of pancytopenia among workers with significant exposure (Goldstein, 1983). The connection between myelotoxicity and acute myelogenous leukemia remains a subject of considerable discussion. Blood diseases associated with benzene exposure include pancytopenia (most frequently cited), leukopenia, bone marrow hypoplasia or aplasia, thrombocytopenia, granulocytopenia, and lymphocytopenia (IARC, 1982; Infante, 1978; Infante and White, 1983; Grossenbacher and Lob, 1982). Benzene, a myelotoxic chemical, causes pancytopenia and eventual aplastic anemia in most animal species exposed.

Ever since Santesson (1897) and Selling (1916) recorded that benzene could cause aplastic anemia, numerous supporting reports have been published (IARC, 1982). The correlation of exposure levels to specific hematologic toxicity has been well documented; however, it is not possible to reliably predict effects produced at specific exposure levels. Likewise, it has not been possible to establish with certainty the degree of exposure below which no adverse hematologic effects in humans would occur.

Effects in humans from benzene exposure have been well characterized and described in medical, toxicology, and poisoning treatment manuals and texts. Although the benzene-associated signs and symptoms in humans cannot be related exactly or with critical accuracy, the biologic events that occur in humans from increasing relatively short-term exposure to benzene appear to follow a pattern from effects on the hematopoietic system, through narcosis, and death. Loss of consciousness, irregular heartbeat, dizziness, headache, and nausea were observed in workers exposed to benzene at concentrations below 20,000 ppm (Deutsche Forschungsgemeinschaft, 1974). Reports that single exposures at concentrations of 20,000 ppm were fatal within 5-10 minutes have been made (Flury, 1928). Continued exposure of workers to benzene has been associated with decreased concentrations of circulating erythrocytes, leukocytes, and thrombocytes (Snyder and Kocsis, 1975). The incidence of sister-chromatid exchanges was not significantly increased in the lymphocytes of 22 workers in Italy exposed to benzene at 0.2-12.4 ppm (mean exposure time, 11.4 years) in air as compared with persons living in the same area of similar age and smoking habits (Sarto, 1984). The incidence of chromosome-type chromosomal aberrations was significantly greater among exposed workers compared with controls.

Although a link between benzene exposure and hematologic disorders was suggested 80 years ago, a connection with leukemia was not clearly established at that time. In early epidemiologic studies, workers were exposed to other chemicals in addition to benzene (Infante, 1978; IARC, 1982; Grossenbacher and Lob, 1982).

An association between long-term exposure to benzene and the occurrence of leukemia was suggested as early as 1928 by Delore and Borgomano, who described acute lymphoblastic leukemia in a worker exposed to benzene for 5 years. IARC (1982) gives a chronology of published literature. Goldstein (1977) describes a number of additional case reports. Most malignancies in which an association with exposure to benzene has been reported have been leukemias, particularly those of the myelogenous type. A critical issue in benzene risk assessment seems to center on the interpretation of the shape associated with the dose-response curve relating benzene exposure to acute myelogenous leukemia and variants.

More than 100 occurrences of leukemia in humans have been associated with benzene exposure since 1928 (Delore and Borgomano, 1928; Vigliani, 1976). More recent epidemiologic studies of small cohorts exposed to benzene have

demonstrated a causal association for leukemia (IARC, 1982; Infante et al, 1977; Rinsky et al. 1986; Ott et al., 1978; Decoufle et al., 1983; Aksoy, 1985; Infante and White, 1985). Rinsky et al. (1986) examined the updated mortality of a cohort with occupational exposure to benzene and calculated a cumulative benzene exposure index (parts per million × years) for each cohort member. These authors found that the standard mortality ratio (SMR) for leukemia was 328 and for multiple myeloma was 398. With stratification of the cohort by cumulative exposure, the SMR's for leukemia increased from 105 in workers with less than 40-ppm-years' exposure to 314 in workers with 40- to 199-ppm-years, to 1,757 in those with from 200- to 399-ppm-years, and to 4,535 in those with 400-ppm-years or more. Most of these studies are summarized in the December 1985 Federal Register notice on occupational exposure to benzene (Fed. Reg., 1985) and to a lesser degree by Goldstein (1985).

STUDY RATIONALE

Benzene was studied for long-term effects in rodents by the NTP Carcinogenesis Program because of its large production volume, because of epidemiologic evidence that exposure of humans to benzene is associated with an increased incidence of leukemia, and because previous experimental studies for carcinogenicity in laboratory animals were considered to be inconclusive or inadequate. In the studies reported in this Technical Report, benzene was given by gavage in corn oil because the chemical was only slightly soluble in water, because benzene was considered too volatile to be administered by feed, and to make certain that the animals would be exposed to a sufficient and accurately calculated amount of the chemical. In retrospect, the inhalation route may have been a more appropriate mimic of human exposure.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZENE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SEVENTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Hematologic Analyses

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

Statistical Analysis of Benzene Hematology Data

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZENE

Benzene was obtained from Burdick and Jackson Laboratories (Muskegon, Michigan). Lot numbers AB223 and AB490 were used for both the 17-week and 2-year studies. A comparison of the two lots by gas chromatography indicated both were similar. Thereafter, lot no. AB223 was used as a reference to identify both lots.

Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix H). Results of elemental analyses for carbon and hydrogen agreed with the theoretical values. Four impurities with a total area 0.2% that of the major peak were detected by gas chromatography in one system. Five impurities with a total area less than 0.09% that of the major peak were detected by a second gas chromatographic system. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those in the literature. Benzene was stored in its original container at room temperature. Results of periodic analyses of the bulk chemical by gas chromatography and infrared spectroscopy indicated that the chemical was stable throughout these studies. The benzene used in these studies was greater than 99.7% pure.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

A weighed amount of benzene was mixed with the appropriate amount of Mazola® corn oil and mixed by inversion (Appendix I).

Benzene in corn oil was found to be stable at 25° C for at least 7 days (Appendix I). Dose mixtures were routinely used within 2 weeks of preparation. All benzene/corn oil mixtures analyzed were within ± 10% of the target concentrations (Appendixes J and K).

SEVENTEEN-WEEK STUDIES

Seventeen-week studies were conducted to evaluate the cumulative toxicity of benzene and to determine the doses to be used in the 2-year studies. Four-week-old F344/N rats and 6-week-old $B6C3F_1$ mice of each sex were obtained from Charles River Breeding Laboratories, observed for 15 days, and then assigned to cages according to a table of random numbers. Cages were then assigned to vehicle control and dosed groups according to another table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 25, 50, 100, or 400 mg/kg benzene in corn oil by gavage, 5 days per week for 17 weeks. Groups of 15 rats and 15 mice of each sex were administered 0, 200, or 600 mg/kg.

Rats and mice were housed five per cage. Feed and water were freely available. Animals were checked twice daily; moribund animals were killed. Animal weights were recorded weekly. Further experimental details are summarized in Table 3.

Five rats and five mice of each sex were killed on day 0. On day 60, five rats and five mice of each sex from the 0, 200, and 600 mg/kg groups were killed. The hematologic analyses performed on blood taken from the orbital sinuses of these animals are listed in Table 3. At the end of the 120-day studies, survivors were killed and hematologic analyses were performed on five animals from each group. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 3.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 50, 100, or 200 mg/kg benzene in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 female rats and 50 mice of each sex were administered 0, 25, 50, or 100 mg/kg. Blood was withdrawn from 10 randomly preselected animals from each sex and dose group (nos. 41-50) at 12, 15, 18, and 21 months. Blood was also taken from moribund animals before they were killed and from all animals at the terminal kill at 24 months. Additional groups of 10 animals of each sex and species were administered benzene for 51 weeks at the doses of the 2-year studies; blood was withdrawn at 0, 3, 6, 9, and 12 months; these animals were killed and necropsies were performed.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZENE

	Seventeen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Test Groups	10 or 15 males and 10 or 15 females of each species	60 males and 60 females of each species
Doses	0, 25, 50, 100, 200, 400, or 600 mg/kg benzene in corn oil; dose vol--5 ml/kg	Rats--0, 50, 100, or 200 mg/kg (males); 0, 25, 50, or 100 mg/kg (females); mice--0, 25, 50, or 100 mg/kg benzene in corn oil by gavage; dose vol--5 ml/kg
Date of First Dose	10/14/78	Rats--12/10/79; mice--1/8/80
Date of Last Dose	2/10/79	Rats--11/27/81; mice--12/26/81
Duration of Dosing	5 d/wk for 120 d; 5 d/wk for 60 d for 5 animals from 0, 200, and 600 mg/kg groups	5 d/wk for 103 wk for 50 animals of each sex and species/dose group; 5 d/wk for 51 wk for 10 animals of each sex and species/dose group
Type and Frequency of Observation	Observed 2 × d; animal weights and feed consumption measured 1 × wk	Observed 2 × d; weighed 1 × wk for 13 wk, 1 × mo thereafter
Necropsy and Histologic Examination	The following tissues were examined histologically in the predosing vehicle control, study vehicle control, and interim-kill animals and the 600 mg/kg animals at terminal kill: mandibular lymph node, salivary glands, femur, thyroid gland, parathyroid, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, lungs and mainstem bronchi, mammary gland, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland; in addition, spleens were examined in all dose groups; special hematology and histology studies performed on animals killed at d 0 and d 60 and on 5 animals/group at 0, 200, and 600 mg/kg at terminal kill and on any animals killed in a moribund condition; coagulation times and hematology analyses performed: hemoglobin, hematocrit, white blood cell count, red blood cell count, mean corpuscular volume, and reticulocyte count	10 animals of each sex and species/dose group received a hematologic exam at 12, 15, 18, and 21 mo; 10 animals of each sex and species/dose group received an abbreviated hematologic exam at 0, 3, 6, and 9 mo prior to complete hematologic exam at 12-mo kill; all survivors at 104 wk received complete hematology profile. The following tissues were examined histologically: gross lesions and tissue masses, mandibular or mesenteric lymph node, salivary glands, sternebrae, femur, or vertebrae including marrow, thyroid gland, thymus, parathyroids, liver, small intestine, colon, gallbladder (mice), brain, prostate/testes or ovaries/uterus, skin, heart, esophagus, stomach, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord, eyes, mammary gland, lungs/mainstem bronchi
ANIMALS AND ANIMAL MAINTENANCE		
Testing Laboratory	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZENE (Continued)

	Seventeen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Time Held Before Test	15 d	19 d
Age When Placed on Study	Rats--6 wk; mice--8 wk	Rats--7-8 wk; mice--6.5-8.5 wk
Age When Killed	120-d kill: rats--25 wk; mice--27 wk; 60-d kill: rats--15 wk; mice--17 wk	111-112 wk
Necropsy Dates	120-d kill: rats--2/12/79-2/13/79; mice--2/14/79-2/15/79	Rats--12/7/81-12/11/81; mice--1/4/82-1/8/82
Method of Animal Distribution	According to two tables of random numbers	Assigned to cages; then to groups using two tables of random numbers
Feed	Purina Lab Chow 5001 (pellets) (Ralston-Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Ziegler Bros, Gardners, PA); freely available
Bedding	Absorb-Dri® (Lab Products, Inc., Rochelle Park, NJ)	Same as 17-wk studies
Water	Automatic Watering System (Edstrom Industries, Waterford, WI); freely available	Same as 17-wk studies
Cages	Polycarbonate (Lab Products, Inc., Rochelle, Park, NJ)	Same as 17-wk studies
Cage Filters	Spun-bonded polyester (Snow Filtration Co., Cincinnati, OH)	Same as 17-wk studies
Animals Per Cage	5	5
Animal Room Environment	Temp--22° ± 1° C; humidity--40%-65%; fluorescent light 12 h/d; 15 room air changes/h	Temp--23° ± 3° C; humidity--40%-60%; fluorescent light 12 h/d; 15 room air changes/h
Other Chemicals on Test in Same Room	None	None
CHEMISTRY		
Lot Numbers Used	AB223	AB223/AB490
Supplier	Burdick and Jackson Laboratories (Muskegon, MI)	Same as 17-wk studies
Date of Initial Use of Subsequent Lots	N/A	Lots used interchangeably
CHEMICAL/VEHICLE		
Preparation	Mixed on a w/v basis with corn oil in a graduated cylinder and stirred for 5 min	Mixed on a w/v basis with corn oil in a graduated cylinder and inverted 21 times
Maximum Storage Time	14 d	14 d
Storage Conditions	In glass containers at room temperature	Same as 17-wk studies

Hematologic Analyses

Hematologic analyses included packed cell volume, red blood cell count, total and differential white blood cell count, hemoglobin, and mean corpuscular volume. Reticulocyte count and prothrombin time (PRT) were also determined.

Blood for interim hematologic analyses was drawn from unanesthetized animals by retro-orbital bleeding. Blood was drawn by cardiac puncture from pentobarbital-anesthetized moribund animals and animals at the 12- and 24-month terminal kills. Blood was collected in Microtainer® tubes (Becton-Dickinson) that contained anticoagulants: sodium citrate for PRT determinations and EDTA for all other analyses. Samples were gently inverted on an aliquot mixer to insure proper mixing and to prevent clotting before analysis on a Coulter Counter Model FN or an Ortho ELT-8 Laser Hematology Analyzer. Smears for differential cell counts were made from the EDTA blood and were stained on an Ames Hema-Tek® Slide Stainer by a modified Wright-Giemsa stain. Reticulocytes were counted after they were stained with New Methylene Blue N. The PRT was determined by a BBL FibroSystem® with Ortho Brain Thromboplastin®.

Three groups of rats and mice were designated for hematologic assessment in the study:

Group A—Forty animals of each species, sex, and dose group were bled at the 24-month kill.

Group B—Ten animals of each species, sex, and dose group were bled orbitally at 12, 15, 18, and 21 months and at the termination of the study at 24 months.

Group C—Ten animals of each species, sex, and dose group were bled orbitally at 0 (before dosing), 3, 6, and 9 months and at the termination of the study at 12 months.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in this study were produced under strict barrier conditions at the Charles River Breeding Laboratories (Portage, Michigan) under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the testing laboratory at 4-5 weeks of age. The animals were quarantined at the testing facility for 2 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and the mice at 6.5-8.5 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

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

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

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

Animal Maintenance

Animals were housed five per cage. Feed and water were freely available. Details of animals maintenance are summarized in Table 3.

Clinical Examinations and Pathology

All animals were observed twice per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. 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.

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. Tissues examined microscopically are listed in Table 3.

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 tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance 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 coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and the PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

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

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

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number

of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) before histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

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

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

Life Table Analyses—The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses—The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the 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 tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time intervals. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

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

Statistical Analysis of Benzene Hematology Data

Initially, a procedure outlined by Dixon and Massey (1951) was used to screen for outliers in dose groups at each point in time. In addition,

data resulting from rebleeding of animals were excluded from statistical analyses.

Since the same animals were examined across time, a repeated measures analysis of variance (Winer, 1971) was considered to be an appropriate method to investigate temporal and dose-related variation. This analysis results in a table of the following form which is useful in assessing the significance of systematic sources of variation in the data:

Source	DF	MS	F	Prob >F
Dose	--	--	--	--
Animal (Dose)	--	--		
Time	--	--	--	--
Dose × Time	--	--	--	--
Error	--	--		

In this table, values of F statistics for dose, time, and dose by time interaction reflect the degree of systematic variation in these sources relative to the random variability exhibited by the data. Because of the repeated-measurement nature of the experiment, there are two sources of random variability. The first, animal (dose), reflects the random variation among animals in dose groups estimated across time. By dividing the mean square (MS) for dose by the MS associated with animal (dose), the value of an F statistic is computed. Time- and dose × time-interaction F statistics are computed using the "Error" MS as the denominator. "DF" in the table refers to the degrees of freedom associated with each source of variation.

The significance levels (P values) associated with dose, time, and dose × time are listed in the column "Prob >F." Small values ($P<0.05$) can be interpreted as follows:

Dose: Variation in measurements is related to differences in dose.

Time: Measurements vary systematically with time.

Dose × Time: Dose effects differ at various points in time.

Because different animals were used in the three time periods (months 0-12, months 12-24, month 24) and because of differences in methods of bleeding and in instrumentation, six separate analyses of variance were performed for each hematologic parameter. Analyses of variance were performed for the following subgroups: months 0-3 (Coulter Counter), months 6-9 (orbital bleeding), group B at month 12 (bleeding by cardiac puncture, animals off dose for 3 days), group C from months 12 to 21 (orbital bleeding), group C at month 24 (bleeding 1 week after cessation of dosing), and group A at month 24 (bleeding 1 week after cessation of dosing). For groups A (month 24) and B at months 12 and 24, these were simple one-way analyses of variance.

The analyses of variance were performed primarily to assess the significance of compound effects and systematic temporal variability. In addition, the analyses of variance provided error variance estimates for Dunnett's multiple comparison procedure (1955, 1964). This technique was employed to contrast vehicle control and dosed group means at each hematologic-measurement time using the error mean square as a pooled estimate of variance. In the application of the procedure, comparisons were two-sided and significance was assessed at both $P=0.01$ and $P=0.05$. The results of Dunnett's procedure are reported with descriptive statistics (mean, standard error, sample size) for dose groups at time of hematologic examination. Means and standard errors are also plotted against time with dashed vertical lines representing the six time periods corresponding to the analyses of variance.

III. RESULTS

RATS

SEVENTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

Hematologic Analyses

MICE

SEVENTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

Hematologic Analyses

SEVENTEEN-WEEK STUDIES

No compound-related deaths occurred. Final mean body weights (relative to those of the vehicle controls) were depressed 14%-22% for male and female rats that received 200, 400, or 600 mg/kg benzene (Table 4).

A dose-related leukopenia was observed for both male and female rats (Appendix M, Table M1). Lymphoid depletion in the B-cell of the spleen was observed in 3/5 male and 4/5 female rats that received 200 mg/kg benzene and 5/5 male and 5/5 female rats that received 600 mg/kg benzene for 60 days and in 10/10 male and 10/10 female rats that received 600 mg/kg for 120 days. Increased extramedullary hematopoiesis was observed in the spleen of 4/5 male and 3/5 female rats that received 600 mg/kg for 120 days.

Based on these composite observations, doses selected for rats for the 2-year studies were 50, 100, or 200 mg/kg benzene in corn oil for males and 25, 50, or 100 mg/kg for females.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Dose-related weight gain reduction, with earlier and more pronounced differences, occurred at higher doses (Table 5 and Figure 2). After week 22, mean body weights of dosed male rats were lower than those of the vehicle controls; the 200 mg/kg group had body weights that were 11% lower than vehicle controls at week 25 and that continued to be lower until the difference was 23% at week 103. The low dose group was comparable to vehicle controls throughout the study; the mid dose group showed about a 7%-9% lower body weight after 1 year. After week 62, mean body weights of high dose female rats were lower than those of the vehicle controls. Only the 100 mg/kg group showed reductions greater than 5% and yet the maximum difference (−9.5%) occurred at week 103.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SEVENTEEN-WEEK GAVAGE STUDIES OF BENZENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	137 ± 6	366 ± 5	+229 ± 6	--
25	10/10	113 ± 2	352 ± 6	+239 ± 6	96
50	10/10	127 ± 6	357 ± 4	+230 ± 6	98
100	10/10	124 ± 5	340 ± 6	+216 ± 8	93
200	10/10	126 ± 6	314 ± 8	+188 ± 7	86
400	10/10	110 ± 2	294 ± 7	+184 ± 8	80
600	(d) 9/10	117 ± 4	285 ± 5	+166 ± 4	78
FEMALE					
0	10/10	88 ± 2	199 ± 4	+111 ± 3	--
25	10/10	82 ± 3	187 ± 3	+105 ± 3	94
50	10/10	75 ± 3	182 ± 4	+107 ± 2	91
100	10/10	101 ± 2	187 ± 2	+ 86 ± 3	94
200	10/10	80 ± 3	168 ± 4	+ 88 ± 4	84
400	10/10	87 ± 4	170 ± 5	+ 83 ± 6	85
600	10/10	78 ± 3	159 ± 2	+ 81 ± 3	80

(a) Number surviving/number in group
(b) Initial group mean body weight. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors ± standard error of the mean
(d) Cause of death not known

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

Weeks on Study	Veh Control Av Wt (grams)	Veh Control No. of Survivors	Low Dose Av Wt (grams)	Low Dose Wt (percent of veh cont)	Low Dose No. of Survivors	Mid Dose Av Wt (grams)	Mid Dose Wt (percent of veh cont)	Mid Dose No. of Survivors	High Dose Av Wt (grams)	High Dose Wt (percent of veh cont)	High Dose No. of Survivors
MALE	**Vehicle Control**		**50 mg/kg**			**100 mg/kg**			**200 mg/kg**		
(a) 0	151	60	154	102	60	154	102	60	155	103	60
1	187	60	187	100	59	186	99	60	185	99	60
2	213	60	212	100	59	211	99	60	209	98	60
3	236	60	236	100	59	233	99	60	232	98	60
4	253	60	254	100	59	253	100	60	248	98	60
5	268	60	268	100	59	269	100	60	266	99	60
6	285	60	284	100	59	285	100	60	278	98	60
7	296	60	287	97	59	296	100	60	287	97	60
8	303	60	300	99	59	305	101	60	298	98	60
9	311	60	307	99	59	311	100	60	302	97	60
10	320	60	315	98	59	318	99	60	307	96	60
11	326	60	321	98	59	326	100	60	312	96	60
12	336	59	337	100	59	333	99	60	323	96	60
17	366	59	358	98	59	357	98	60	339	93	60
22	391	59	383	98	59	379	97	60	359	92	60
26	405	58	393	97	59	385	95	60	360	89	60
30	409	57	400	98	59	396	97	60	365	89	60
35	438	55	417	96	58	408	94	60	378	87	60
39	445	54	424	95	58	415	93	60	377	85	60
43	447	53	418	94	58	423	95	60	387	87	59
48	464	53	434	94	57	424	91	60	385	83	59
52	461	43	436	95	47	427	93	49	381	83	49
57	465	43	444	95	46	436	94	49	395	85	49
62	474	41	442	93	45	432	91	48	387	82	49
66	481	41	449	93	44	436	91	48	394	82	48
71	484	40	457	94	43	443	92	46	405	84	48
75	490	39	465	95	42	446	91	42	402	82	47
79	478	39	461	96	42	445	93	41	398	83	46
83	494	37	470	95	40	450	91	38	397	80	45
87	487	36	464	95	40	444	91	35	389	80	37
92	489	35	467	96	38	442	90	31	388	79	30
96	478	35	463	97	37	439	92	28	388	81	23
100	477	34	453	95	34	432	91	26	375	79	18
103	467	32	454	97	29	427	91	25	360	77	16
FEMALE	**Vehicle Control**		**25 mg/kg**			**50 mg/kg**			**100 mg/kg**		
(a) 0	113	60	112	99	60	113	100	60	115	102	60
1	132	60	130	98	60	130	98	60	133	101	60
2	140	60	139	99	60	140	100	60	141	101	60
3	150	60	148	99	60	148	99	60	149	99	59
4	157	60	155	99	60	156	99	60	158	101	58
5	165	60	164	99	60	163	99	60	164	99	58
6	169	60	168	99	60	168	99	60	169	100	58
7	174	60	173	99	60	174	100	60	173	99	58
8	176	60	176	100	60	176	100	60	175	99	58
9	179	60	178	99	60	180	101	60	178	99	58
10	180	60	180	100	60	181	101	60	183	102	57
11	182	60	183	101	60	185	102	60	184	101	57
12	183	60	184	101	60	184	101	60	185	101	57
17	194	60	193	99	60	196	101	60	196	101	57
22	200	60	199	100	60	199	100	60	200	100	57
26	208	60	208	100	60	206	99	60	204	98	57
30	211	60	212	100	60	209	99	60	209	99	57
35	222	59	219	99	60	222	100	60	218	98	56
39	225	59	222	99	60	225	100	60	216	96	56
43	228	59	225	99	59	226	99	60	222	97	56
48	233	59	230	99	59	230	99	59	225	97	56
52	238	49	231	97	49	232	97	48	226	95	47
57	243	49	243	100	49	243	100	48	236	97	46
62	258	49	250	97	49	251	97	48	240	93	45
66	260	49	253	97	49	252	97	47	243	93	44
71	263	49	258	98	48	260	99	45	252	96	43
75	273	49	264	97	48	264	97	43	256	94	41
79	281	49	272	97	47	269	96	42	259	92	41
83	294	49	284	97	44	280	95	41	271	92	39
87	295	49	284	96	44	282	96	41	269	91	39
92	300	49	290	97	42	287	96	40	274	91	38
96	296	48	292	99	41	287	97	39	273	92	36
100	302	47	298	99	40	289	96	38	271	90	30
103	304	46	301	99	38	288	95	35	275	90	26

(a) Mean body weights 2 days after first dose

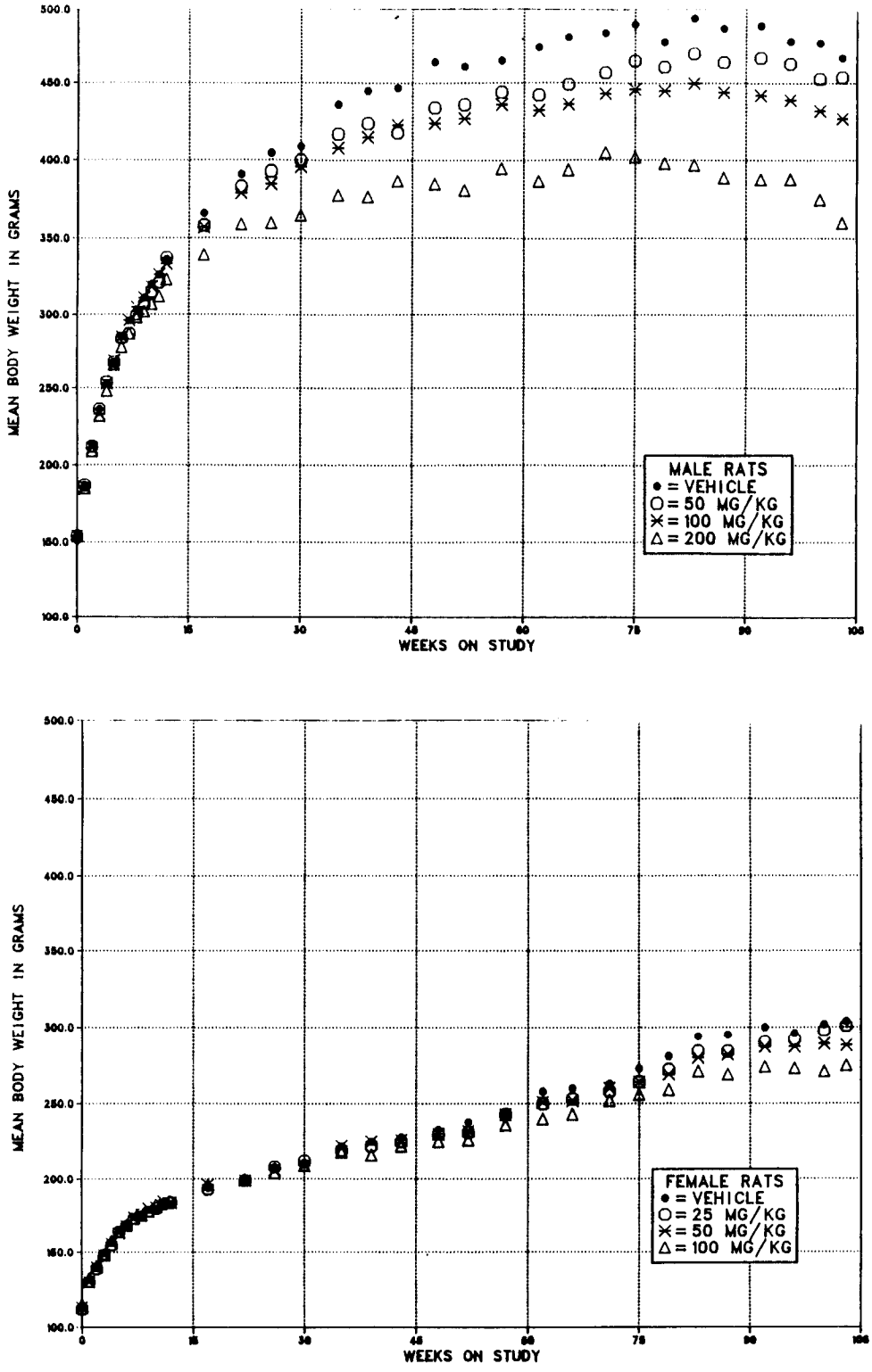


FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED BENZENE IN CORN OIL FOR TWO YEARS

Other than modest decreases in body weights in each group compared with vehicle controls (except for the 200 mg/kg male rats), no extraordinary clinical signs were recorded. Nonspecific observations included a varying degree of ocular discharge. This common syndrome in F344 rats was first observed at 4-5 months in both sexes and across groups. A serous discharge varying from clear to red-tinged or yellow and from scant to heavy occurred in about 10% of all rats; this may have been associated with blood sampling techniques. Near the end of the studies, a paleness of mucosa was recorded for rats in a moribund state before death.

Survival

Estimates of the probabilities of the survival of male and female rats administered benzene at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 3. The survival of the high dose group of male rats was significantly lower than that of the vehicle control group after week 95 (Table 6). In females, the survival of both the mid dose after week 101 and high dose groups after week 96 was significantly lower than that of the vehicle control group; this latter group had exceptionally good survival (92%) compared with the historical rate of 74% ± 7% (SD) (Haseman et al., 1985).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidence of rats with neoplastic or nonneoplastic lesions in the Zymbal gland, palate, lip, tongue, skin, uterus, uterus/endometrium, spleen, thymus, cardiac stomach, adrenal gland, thyroid gland, and pituitary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the four groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 6. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	12	18	19	30
Accidentally killed (c)	6	3	6	4
Killed at termination	32	29	24	16
Died during termination period	0	0	1	0
Survival P values (d)	0.001	0.431	0.253	0.003
FEMALE (a)	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**	**100 mg/kg**
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	4	10	14	20
Accidentally killed (c)	0	2	2	5
Killed at termination	46	38	33	25
Died during termination period	0	0	1	0
Survival P values (d)	0.001	0.125	0.014	<0.001

(a) Terminal kill period: week 104
(b) Includes animals killed in a moribund condition
(c) Cause of death not known
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

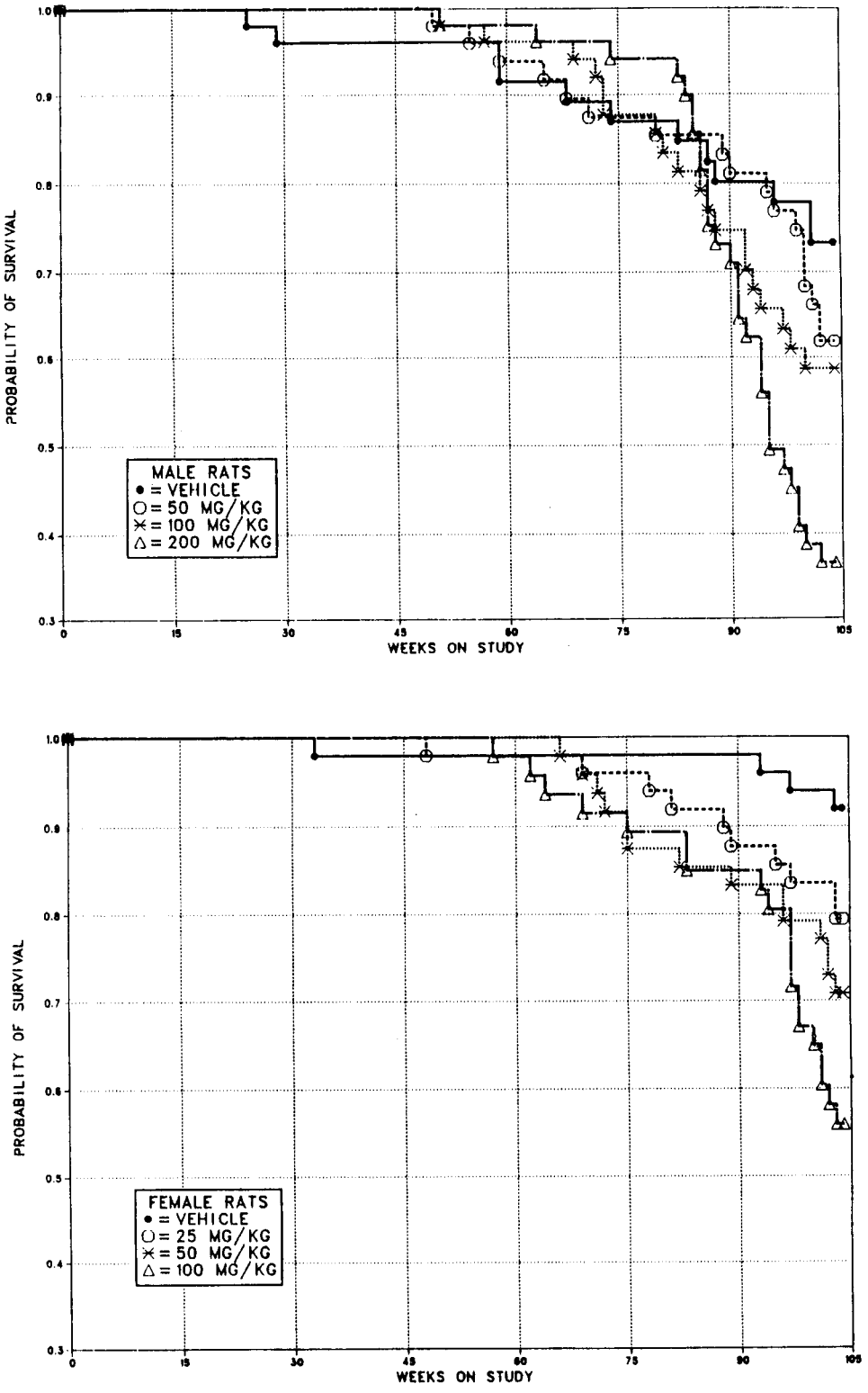


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED BENZENE IN CORN OIL FOR TWO YEARS

Zymbal Gland: Hyperplasia or squamous metaplasia of the Zymbal gland was increased in low dose males and in mid dose and high dose females (Table 7). The incidences of ductal dilatation in males (vehicle control, 8/32; low dose, 35/46; mid dose, 20/42; high dose, 28/42) and in females (15/45; 22/40; 28/44; 23/46) were increased as were those of cystic ducts (male: vehicle control, 1/32; low dose, 7/46; mid dose, 6/42; high dose, 0/42; female: 1/45; 2/40; 8/44; 3/46). Carcinomas in males and females occurred with significant positive trends, and the incidences in the mid dose and high dose males and dosed females were significantly greater than those in the vehicle controls.

Grossly, these lesions appeared on the side of the head adjacent to or involving the ear and were up to 6 cm in diameter. The interior of the tumor was soft, yellow to white, and occasionally gritty. Microscopically, the tumors contained various amounts of epithelial and sebaceous elements and were classified as adenomas or carcinomas. Rarely, Zymbal gland neoplasms contained significant spindle-cell components; these were classified as carcinosarcomas, and one was found in a 50 mg/kg female rat. Although they vary histologically, these tumors are considered to be part of the spectrum of Zymbal gland tumors.

TABLE 7. ANALYSIS OF ZYMBAL GLAND LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE (a)

MALE	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Hyperplasia				
Overall Rates	(b) 0/32 (0%)	6/46 (13%)	2/42 (3%)	3/42 (7%)
Adenoma				
Overall Rates	0/32 (0%)	1/46 (2%)	0/42 (0%)	1/42 (2%)
Carcinoma				
Overall Rates	2/32 (6%)	6/46 (13%)	10/42 (24%)	17/42 (40%)
Adjusted Rates	7.2%	15.4%	28.8%	55.6%
Terminal Rates	1/22 (5%)	2/28 (7%)	2/21 (10%)	5/15 (33%)
Life Table Tests	P<0.001	P=0.193	P=0.017	P<0.001
Incidental Tumor Tests	P=0.003	P=0.352	P=0.214	P=0.024
Adenoma or Carcinoma (c)				
Overall Rates	2/32 (6%)	7/46 (15%)	10/42 (24%)	18/42 (43%)
Adjusted Rates	7.2%	18.7%	28.8%	57.0%
Terminal Rates	1/22 (5%)	3/28 (11%)	2/21 (10%)	5/15 (33%)
Life Table Tests	P<0.001	P=0.131	P=0.017	P<0.001
Incidental Tumor Tests	P=0.002	P=0.247	P=0.214	P=0.019
FEMALE	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**	**100 mg/kg**
Hyperplasia				
Overall Rates	0/45 (0%)	0/40 (0%)	6/44 (14%)	(b) 1/46 (2%)
Adenoma				
Overall Rates	0/45 (0%)	0/40 (0%)	1/44 (2%)	1/46 (2%)
Carcinoma				
Overall Rates	0/45 (0%)	5/40 (10%)	5/44 (11%)	14/46 (30%)
Adjusted Rates	0.0%	13.3%	14.4%	42.0%
Terminal Rates	0/41 (0%)	3/33 (9%)	3/29 (10%)	8/25 (32%)
Life Table Tests	P<0.001	P=0.022	P=0.018	P<0.001
Incidental Tumor Tests	P<0.001	P=0.036	P=0.067	P<0.001
Adenoma or Carcinoma (d)				
Overall Rates	0/45 (0%)	5/40 (13%)	(e) 6/44 (14%)	15/46 (33%)
Adjusted Rates	0.0%	13.3%	16.2%	45.4%
Terminal Rates	0/41 (0%)	3/33 (9%)	4/29 (14%)	9/25 (36%)
Life Table Tests	P<0.001	P=0.022	P=0.010	P<0.001
Incidental Tumor Tests	P<0.001	P=0.036	P=0.021	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) One vehicle control male rat and two high dose female rats had squamous metaplasia.
(c) Historical incidence at laboratory (mean): 0/100; historical incidence in NTP studies: 4/1,146 (0.3%)
(d) Historical incidence at laboratory (mean): 1/100 (1%); historical incidence in NTP studies: 5/1,147 (0.4%)
(e) A carcinosarcoma was observed in a seventh mid dose female rat, and a squamous cell papilloma of the ear was observed in an eighth mid dose female rat.

Palate, Lip, and Tongue: The numbers of rats with squamous cell neoplasms of the palate, lip, or tongue are given in Table 8. Squamous cell papillomas, squamous cell carcinomas, and squamous cell papillomas or carcinomas (combined) of the palate, lip, or tongue (separately and combined in males and combined in females) occurred with significant positive trends (Table 9).

Neoplasms of the tongue appeared grossly as raised papillary masses on the dorsal surface. These lesions were well differentiated and contained primarily squamous cells and were classified as either squamous cell papillomas or squamous cell carcinomas depending on whether invasion of adjacent structures had occurred.

Lesions of the lip had a similar microscopic appearance to those neoplasms of the skin and others at the mucocutaneous junction. Although separated topographically, these can be combined with skin tumors for biologic interpretation.

TABLE 8. NUMBER OF RATS WITH SQUAMOUS CELL NEOPLASMS OF THE PALATE, LIP, AND TONGUE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE (a)

	Male				Female			
Site	0	50 mg/kg	100 mg/kg	200 mg/kg	0	25 mg/kg	50 mg/kg	100 mg/kg
No. of Rats Examined	50	50	50	50	50	50	50	50
Palate								
Papilloma	0	4	4	9	1	3	5	3
Carcinoma	0	0	1	0	0	1	0	1
Papilloma or carcinoma	0	4	5	9	1	4	5	4
Tongue								
Papilloma	1	0	2	2	0	1	1	0
Carcinoma	0	3	4	4	0	0	4	4
Papilloma or carcinoma	1	3	6	6	0	1	5	4
Lip								
Papilloma	0	2	5	5	0	0	2	2
Carcinoma	0	0	0	3	0	0	0	0
Papilloma or carcinoma	0	2	5	8	0	0	2	2
Palate, Tongue, or Lip								
Papilloma	1	6	11	13	1	4	8	5
Carcinoma	0	3	5	7	0	1	4	5
Papilloma or carcinoma	1	9	16	19	1	5	12	9

(a) Results of statistical analyses are shown in Table 9.

TABLE 9. ANALYSIS OF PALATE, LIP, AND TONGUE TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

MALE	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Palate: Squamous Cell Papilloma				
Overall Rates	0/50 (0%)	4/50 (8%)	4/50 (8%)	9/50 (18%)
Adjusted Rates	0.0%	11.4%	11.7%	37.8%
Terminal Rates	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests	P<0.001	P=0.064	P=0.057	P<0.001
Incidental Tumor Tests	P=0.005	P=0.098	P=0.142	P=0.006
Palate: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Palate: Squamous Cell Papilloma or Carcinoma				
Overall Rates	0/50 (0%)	4/50 (8%)	5/50 (10%)	9/50 (18%)
Adjusted Rates	0.0%	11.4%	13.6%	37.8%
Terminal Rates	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests	P<0.001	P=0.064	P=0.034	P<0.001
Incidental Tumor Tests	P=0.005	P=0.098	P=0.097	P=0.006
Lip: Squamous Cell Papilloma				
Overall Rates	0/50 (0%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted Rates	0.0%	6.9%	20.0%	23.9%
Terminal Rates	0/32 (0%)	2/29 (7%)	5/25 (20%)	3/16 (19%)
Life Table Tests	P=0.001	P=0.216	P=0.015	P=0.008
Incidental Tumor Tests	P=0.004	P=0.216	P=0.015	P=0.027
Lip: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	0.0%	17.4%
Terminal Rates	0/32 (0%)	0/29 (0%)	0/25 (0%)	2/16 (13%)
Life Table Tests	P=0.002	(a)	(a)	P=0.035
Incidental Tumor Tests	P=0.008	(a)	(a)	P=0.091
Lip: Squamous Cell Papilloma or Carcinoma				
Overall Rates	0/50 (0%)	2/50 (4%)	5/50 (10%)	8/50 (16%)
Adjusted Rates	0.0%	6.9%	20.0%	39.2%
Terminal Rates	0/32 (0%)	2/29 (7%)	5/25 (20%)	5/16 (31%)
Life Table Tests	P<0.001	P=0.216	P=0.015	P<0.001
Incidental Tumor Tests	P<0.001	P=0.216	P=0.015	P=0.002
Tongue: Squamous Cell Papilloma				
Overall Rates	1/50 (2%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Tongue: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	0.0%	7.4%	12.8%	17.2%
Terminal Rates	0/32 (0%)	0/29 (0%)	2/25 (8%)	2/16 (13%)
Life Table Tests	P=0.039	P=0.133	P=0.051	P=0.028
Incidental Tumor Tests	P=0.049	P=0.133	P=0.099	P=0.012
Tongue: Squamous Cell Papilloma or Carcinoma				
Overall Rates	1/50 (2%)	3/50 (6%)	6/50 (12%)	6/50 (12%)
Adjusted Rates	2.3%	7.4%	20.4%	24.7%
Terminal Rates	0/32 (0%)	0/29 (0%)	4/25 (16%)	3/16 (19%)
Life Table Tests	P=0.013	P=0.328	P=0.044	P=0.028
Incidental Tumor Tests	P=0.012	P=0.355	P=0.091	P=0.009
Oral Cavity: Squamous Cell Papilloma				
Overall Rates	1/50 (2%)	6/50 (12%)	11/50 (22%)	13/50 (26%)
Adjusted Rates	2.3%	18.0%	37.4%	47.7%
Terminal Rates	0/32 (0%)	4/29 (14%)	8/25 (32%)	5/16 (31%)
Life Table Tests	P<0.001	P=0.058	P=0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.083	P=0.004	P=0.002
Oral Cavity: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	3/50 (6%)	5/50 (10%)	7/50 (14%)
Adjusted Rates	0.0%	7.4%	14.7%	33.0%
Terminal Rates	0/32 (0%)	0/29 (0%)	2/25 (8%)	4/16 (25%)
Life Table Tests	P=0.001	P=0.133	P=0.030	P=0.001
Incidental Tumor Tests	P=0.002	P=0.133	P=0.071	P=0.001

TABLE 9. ANALYSIS OF PALATE, LIP, AND TONGUE TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE (Continued)

MALE (Continued)	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Oral Cavity: Squamous Cell Papilloma or Carcinoma (b)				
Overall Rates	1/50 (2%)	9/50 (18%)	16/50 (32%)	19/50 (38%)
Adjusted Rates	2.3%	24.1%	48.8%	68.6%
Terminal Rates	0/32 (0%)	4/29 (14%)	10/25 (40%)	9/16 (56%)
Life Table Tests	P<0.001	P=0.012	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.014	P<0.001	P<0.001
FEMALE	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**	**100 mg/kg**
Palate: Squamous Cell Papilloma				
Overall Rates	1/50 (2%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates	2.2%	7.9%	13.9%	8.6%
Terminal Rates	1/46 (2%)	3/38 (8%)	4/34 (12%)	1/25 (4%)
Life Table Tests	P=0.103	P=0.240	P=0.053	P=0.183
Incidental Tumor Tests	P=0.183	P=0.240	P=0.101	P=0.620
Palate: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Palate: Squamous Cell Papilloma or Carcinoma				
Overall Rates	1/50 (2%)	4/50 (8%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	2.2%	10.2%	13.9%	11.4%
Terminal Rates	1/46 (2%)	3/38 (8%)	4/34 (12%)	1/25 (4%)
Life Table Tests	P=0.060	P=0.131	P=0.053	P=0.088
Incidental Tumor Tests	P=0.219	P=0.153	P=0.101	P=0.509
Lip: Squamous Cell Papilloma				
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Tongue: Squamous Cell Papilloma				
Overall Rates	0/50 (0%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Tongue: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	9.6%	12.7%
Terminal Rates	0/46 (0%)	0/38 (0%)	0/34 (0%)	1/25 (4%)
Life Table Tests	P=0.004	(b)	P=0.047	P=0.024
Incidental Tumor Tests	P=0.167	(b)	P=0.240	P=0.233
Tongue: Squamous Cell Papilloma or Carcinoma				
Overall Rates	0/50 (0%)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	0.0%	2.6%	11.6%	12.7%
Terminal Rates	0/46 (0%)	1/38 (3%)	0/34 (0%)	1/25 (4%)
Life Table Tests	P=0.010	P=0.462	P=0.025	P=0.024
Incidental Tumor Tests	P=0.274	P=0.462	P=0.240	P=0.233
Oral Cavity: Squamous Cell Papilloma				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	8/50 (16%)	5/50 (10%)
Oral Cavity: Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Oral Cavity: Squamous Cell Papilloma or Carcinoma (c)				
Overall Rates	1/50 (2%)	5/50 (10%)	12/50 (24%)	9/50 (18%)
Adjusted Rates	2.2%	12.8%	28.9%	27.7%
Terminal Rates	1/46 (2%)	4/38 (11%)	6/34 (18%)	4/25 (16%)
Life Table Tests	P<0.001	P=0.068	P<0.001	P=0.001
Incidental Tumor Tests	P=0.039	P=0.081	P=0.007	P=0.029

(a) No P values are reported because no tumors were observed in the vehicle control and 50 mg/kg or 100 mg/kg groups.
(b) Historical incidence of oral cavity tumors (palate, tongue, or oral cavity) at laboratory (mean): 0/100; historical incidence in NTP studies: 2/1,146 (0.2%)
(c) Historical incidence of oral cavity tumors (palate, tongue, or oral cavity) at laboratory (mean): 1/100 (1%); historical incidence in NTP studies: 3/1,147 (0.3%)

Skin: Squamous cell papillomas, squamous cell carcinomas, and squamous cell papillomas or carcinomas (combined) in male rats occurred with significant positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 10).

Neoplasms of the skin were found on the face, back, flank, and other locations. The lesions varied from 1-3 cm in diameter and were raised, ulcerated, and crusty, often with a yellow, friable center. Microscopically, the lesions varied from squamous cell papillomas and squamous cell carcinomas to neoplasms containing various amounts of adnexal structures. If sebaceous, basal, and squamous elements were found, these lesions were classified as adenosquamous adenomas and carcinomas. A few tumors formed primarily hair follicles (classified as trichoepitheliomas), sebaceous elements (classified as sebaceous adenomas), or crater-like epithelial tumors (classified as keratoacanthomas). These tumors represent a spectrum arising from the skin and adnexal tissues and can be combined.

TABLE 10. ANALYSIS OF SKIN TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Squamous Cell Papilloma				
Overall Rates	0/50 (0%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted Rates	0.0%	6.9%	4.0%	27.1%
Terminal Rates	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests	P=0.001	P=0.216	P=0.451	P=0.005
Incidental Tumor Tests	P=0.002	P=0.216	P=0.451	P=0.009
Squamous Cell Carcinoma				
Overall Rates	0/50 (0%)	5/50 (10%)	3/50 (6%)	8/50 (16%)
Adjusted Rates	0.0%	15.3%	9.8%	30.3%
Terminal Rates	0/32 (0%)	3/29 (10%)	0/25 (0%)	2/16 (13%)
Life Table Tests	P<0.001	P=0.032	P=0.098	P=0.001
Incidental Tumor Tests	P=0.069	P=0.064	P=0.278	P=0.039
All Squamous Cell Tumors				
Overall Rates	1/50 (2%)	7/50 (14%)	5/50 (10%)	11/50 (22%)
Adjusted Rates	2.7%	21.8%	17.0%	45.2%
Terminal Rates	0/32 (0%)	5/29 (17%)	2/25 (8%)	5/16 (31%)
Life Table Tests	P<0.001	P=0.031	P=0.076	P<0.001
Incidental Tumor Tests	P=0.017	P=0.055	P=0.221	P=0.012
Squamous Cell Tumors or Undifferentiated Carcinoma (a)				
Overall Rates	1/50 (2%)	7/50 (14%)	5/50 (10%)	12/50 (24%)
Adjusted Rates	2.7%	21.8%	17.0%	47.7%
Terminal Rates	0/32 (0%)	5/29 (17%)	2/25 (8%)	5/16 (31%)
Life Table Tests	P<0.001	P=0.031	P=0.076	P<0.001
Incidental Tumor Tests	P=0.010	P=0.055	P=0.221	P=0.009

(a) Historical incidence at laboratory (mean ± SD): 1/100 (1%); historical incidence in NTP studies: 21/1,146 (2% ± 3%)

Uterus: Incidences of epithelial hyperplasia in dosed and vehicle control female rats were comparable (Table 11). Endometrial stromal polyps occurred with a significant positive trend in female rats, and the incidence in the high dose group was significantly greater than that in the vehicle controls.

Uterus/Endometrium: Endometrial carcinomas were found in two low dose rats, adenomas were found in one low dose rat, and adenocarcinomas were found in two mid dose and two high dose rats; one adenosquamous carcinoma of the cervix was found in a mid dose rat.

Spleen: Lymphoid depletion in the spleen was observed at increased incidences in dosed male and female rats (male: vehicle control, 0/49; low dose, 19/48, 40%; mid dose, 8/47, 17%; high dose, 23/47, 49%; female: vehicle control, 0/50; low dose, 11/50, 22%; mid dose, 8/49, 16%; high dose, 10/49, 20%).

Thymus: Lymphoid depletion was observed at increased incidence in dosed male rats (vehicle control, 0/44; low dose, 4/42, 10%; mid dose, 8/41, 20%; high dose, 10/34, 29%).

Cardiac (nonglandular) Stomach: Hyperkeratosis and acanthosis in the nonglandular forestomach were observed at increased incidences in high dose male rats (hyperkeratosis: vehicle control, 2/48, 4%; low dose, 4/44, 9%; mid dose, 3/48, 6%; high dose, 9/47, 19%; acanthosis: vehicle control, 2/48, 4%; low dose, 4/44, 9%; mid dose, 3/48, 6%; high dose, 10/47, 21%).

Adrenal Gland—Zona Fasciculata: Hyperplasia was observed at increased incidences in low dose rats of each sex (male: vehicle control, 0/50; low dose, 13/49, 27%; mid dose, 0/48; high dose, 2/49, 4%; female: vehicle control, 0/50, low dose, 17/50, 34%; mid dose, 0/47; high dose, 0/49).

TABLE 11. ANALYSIS OF UTERINE LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hyperplasia (Focal, Diffuse, Papillary, or Cystic)				
Overall Rates	33/50 (66%)	35/50 (70%)	34/49 (69%)	35/50 (70%)
Endometrial Stromal Polyp (a)				
Overall Rates	7/50 (14%)	7/50 (14%)	7/49 (14%)	14/50 (28%)
Adjusted Rates	14.8%	17.4%	17.6%	44.5%
Terminal Rates	6/46 (13%)	5/38 (13%)	4/34 (12%)	9/25 (36%)
Life Table Tests	P=0.001	P=0.468	P=0.420	P=0.003
Incidental Tumor Tests	P=0.049	P=0.545	P=0.598N	P=0.049

(a) Historical incidence at laboratory (mean ± SD): 22/98 (22%); historical incidence in NTP studies: 248/1,125 (22% ± 7%)

Thyroid Gland: C-cell adenomas or carcinomas (combined) in male rats occurred with a negative trend (P=0.039) by the incidental tumor test. The incidences in the dosed groups were not significantly different from that in the vehicle control group by the incidental tumor test (vehicle control, 9/49, 18%; low dose, 5/47, 11%; mid dose, 4/46, 9%; high dose, 2/47, 4%). The incidences of C-cell hyperplasia were 7/49 (14%) in the vehicle control, 12/47 (26%) in the low dose, 7/46 (15%) in the mid dose, and 7/47 (15%) in the high dose groups.

Pituitary Gland: Adenomas in male and female rats and carcinomas in male rats occurred with negative trends. The incidences in high dose females and in mid dose and high dose males were lower than those of the vehicle controls. In male rats, the incidence of hyperplasia was as follows: vehicle control, 3/47 (6%); low dose, 7/45 (16%); mid dose, 9/46 (20%); high dose, 5/48 (10%); the incidence of adenomas or carcinomas (combined) was 18/47 (38%) in the vehicle control, 11/45 (24%) in the low dose, 11/46 (24%) in the mid dose, and 7/48 (15%) in the high dose groups. In female rats, the incidence of hyperplasia was as follows: vehicle control, 5/47 (11%); low dose, 10/50 (20%); mid dose, 5/48 (10%); high dose, 7/49 (14%); the incidence of adenomas was 22/47 (47%) in the vehicle control, 15/50 (30%) in the low dose, 15/48 (31%) in the mid dose, and 8/49 (16%) in the high dose groups.

Hematologic Analyses

Hematologic effects were limited to lymphocytopenia. The analyses of variance for groups B and C (Appendix N, Table N4) indicate strong dose effects that varied across time for both males and females. For males, the data suggest a compound-related reduction in lymphocyte count in months 3 through 21 (Figure 4; Table N4). The significance of the interaction term in the analysis of variance for months 12-21 is reflected in temporal changes in the magnitude of differences between vehicle control and dosed groups. Overall, the pattern of response, without regard for magnitude of differences, is consistent across time, suggesting a compound-related depression of lymphocytes in males. There is also evidence of a similar dose-related effect on lymphocytes in females. As in males, differences between dosed and vehicle control means occur in months 3 through 21. However, that pattern of response is not as consistent or dramatic as that seen in the data for males.

A complete statistical analysis of all hematology data is available from the National Toxicology Program. For the benzene hematologic results, the technical quality of certain of these data was questionable; thus, more detailed analyses (e.g., investigation of the association between hematologic and pathologic changes) are deemed inappropriate for these data.

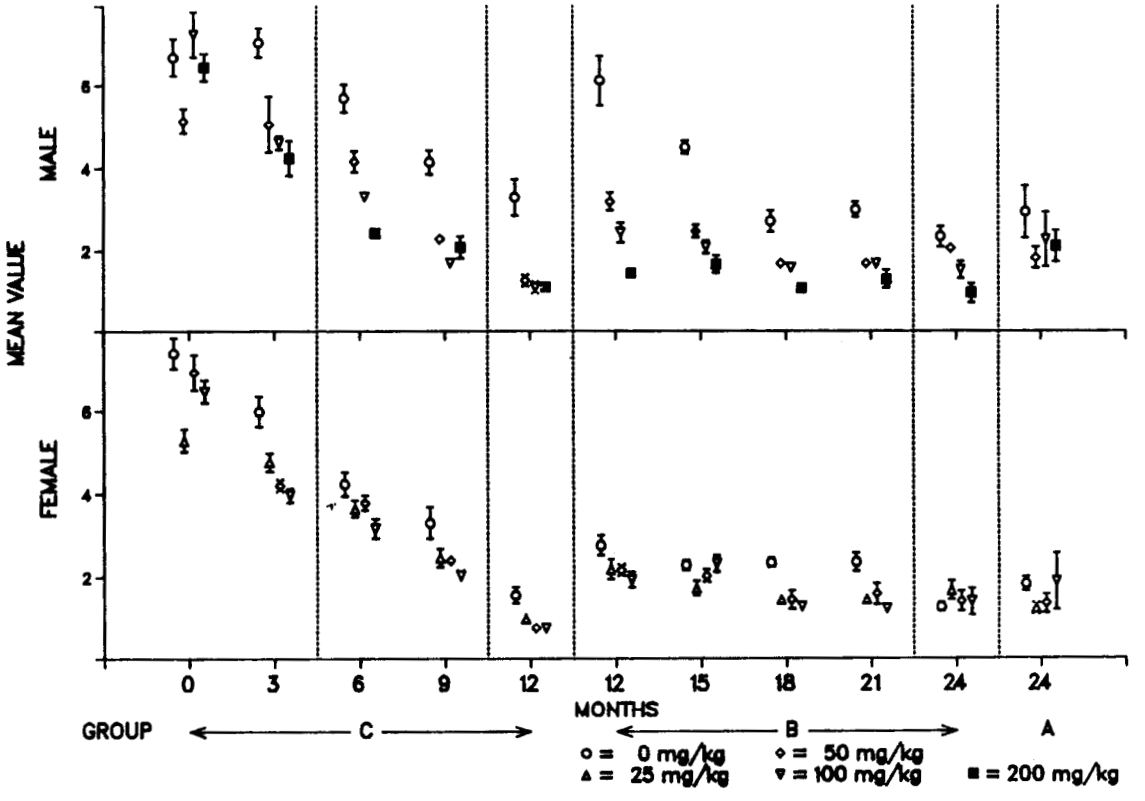


FIGURE 4. RESULTS OF LYMPHOCYTE DETERMINATIONS IN RATS IN THE TWELVE- AND TWENTY-FOUR-MONTH GAVAGE STUDIES OF BENZENE

SEVENTEEN-WEEK STUDIES

No compound-related deaths occurred. Final mean body weights (relative to those of the vehicle controls) were depressed 4%-10% for all dosed groups that received 100 mg/kg or more of benzene (Table 12). Tremors were observed intermittently in the 400 and 600 mg/kg groups throughout the studies, and during the last 3 weeks of the studies, tremors were more pronounced in male mice than in females. A dose-related leukopenia was observed for both male and female mice (Appendix M, Table M2). No compound-related histopathologic effects were observed.

Based on these findings, doses selected for mice for the 2-year studies were 0, 25, 50, and 100 mg/kg benzene in corn oil.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were lower than those of the vehicle controls after week 47, ending in a difference of −19% at 103 weeks (Table 13 and Figure 5). Mean body weights for low and mid dose groups were comparable to those of vehicle controls until about the final 4 or 15 weeks of the study. Mean body weights of vehicle control and high dose female mice were comparable until week 87. From week 87 to the end of the study, mean body weights of high dose female mice were lower than those of the vehicle controls; at week 103, the reduction was 15%. No compound-related clinical signs were observed.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 8/10	23.4 ± 0.5	31.5 ± 1.0	+8.4 ± 0.9	--
25	(d) 8/10	24.7 ± 0.4	31.3 ± 1.0	+6.9 ± 0.7	99
50	10/10	21.8 ± 1.3	30.3 ± 0.6	+8.5 ± 0.9	98
100	10/10	25.7 ± 0.9	30.2 ± 1.6	+4.5 ± 1.4	96
200	(d) 9/10	27.0 ± 0.5	29.4 ± 0.5	+2.2 ± 0.8	93
400	10/10	26.6 ± 0.5	29.9 ± 1.2	+3.3 ± 0.9	95
600	10/10	26.5 ± 0.3	29.4 ± 0.4	+2.9 ± 0.3	93
FEMALE					
0	10/10	17.9 ± 0.3	26.3 ± 0.6	+8.4 ± 0.7	--
25	10/10	20.0 ± 0.3	25.7 ± 0.5	+5.7 ± 0.4	98
50	(d) 9/10	19.6 ± 0.4	25.9 ± 0.8	+6.3 ± 0.2	98
100	10/10	20.0 ± 0.4	24.4 ± 0.7	+4.4 ± 0.6	93
200	10/10	18.8 ± 0.4	24.6 ± 0.4	+5.8 ± 0.3	93
400	(d) 9/10	19.2 ± 0.2	23.8 ± 0.4	+4.6 ± 0.6	90
600	10/10	18.8 ± 0.3	24.3 ± 0.4	+5.5 ± 0.3	92

(a) Number surviving/number in group
(b) Initial group mean body weight. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors ± standard error of the mean
(d) Cause of death not known

TABLE 13. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

Weeks on Study	Veh Control Av Wt (grams)	Veh Control No. of Survivors	25 mg/kg Av Wt (grams)	25 mg/kg Wt (percent of veh cont)	25 mg/kg No. of Survivors	50 mg/kg Av Wt (grams)	50 mg/kg Wt (percent of veh cont)	50 mg/kg No. of Survivors	100 mg/kg Av Wt (grams)	100 mg/kg Wt (percent of veh cont)	100 mg/kg No. of Survivors
MALE											
(a) 0	27.0	60	26.6	99	59	26.1	97	60	26.8	99	60
1	25.8	60	27.1	105	58	27.5	107	60	28.3	110	60
2	27.8	60	28.2	101	58	29.1	105	60	28.8	104	60
3	29.3	58	29.0	99	58	30.2	103	60	29.4	100	60
4	30.4	58	29.9	98	58	30.4	100	60	30.4	100	59
5	30.6	58	30.9	101	58	31.6	103	60	31.4	103	59
6	30.9	58	30.2	98	58	31.3	101	60	31.4	102	59
7	31.6	58	31.1	98	58	32.2	102	60	32.7	103	58
8	33.3	58	32.0	96	58	32.7	98	60	33.0	99	58
9	33.2	58	32.5	98	58	33.3	100	60	31.2	94	58
10	32.9	58	33.1	101	58	33.8	103	60	31.8	97	58
11	34.6	58	33.8	98	58	34.6	100	60	33.6	97	58
12	33.8	58	33.9	100	58	35.2	104	60	34.6	102	58
17	35.8	58	35.2	98	58	36.7	103	60	34.6	97	58
21	37.1	58	36.5	98	58	38.2	103	60	36.3	98	58
25	38.6	58	37.9	98	58	38.6	100	60	36.6	95	57
30	38.9	58	38.4	99	57	39.7	102	59	37.1	95	57
34	40.1	58	39.4	98	57	39.9	100	59	38.1	95	57
38	40.5	57	40.2	99	56	41.3	102	59	38.2	94	57
43	41.5	55	40.2	97	55	42.8	103	58	40.4	97	56
47	44.3	54	44.7	101	54	44.5	100	58	39.8	90	56
52	45.2	54	44.9	99	54	44.7	99	58	41.1	91	56
57	43.6	45	43.2	99	44	42.5	97	48	40.0	92	46
61	43.4	44	43.1	99	44	42.5	98	48	38.8	89	46
66	--	--	--	--	--	42.2	--	46	37.1	--	46
67	42.5	44	42.7	100	44	--	--	--	--	--	--
70	41.5	44	40.2	97	43	41.1	99	45	39.1	94	46
74	41.7	44	42.1	101	42	41.0	98	44	39.2	94	45
78	43.0	43	43.9	102	42	41.9	97	42	39.2	91	42
82	43.5	41	44.1	101	41	42.6	98	42	39.9	92	38
87	42.8	38	43.2	101	36	39.1	91	39	36.9	86	37
91	42.1	38	42.8	102	34	39.5	94	35	35.9	85	32
95	42.2	36	42.1	100	33	39.8	94	30	35.1	83	27
99	41.8	34	40.6	97	30	40.1	96	27	34.2	82	18
103	41.5	29	37.5	90	24	38.0	92	20	33.6	81	7
FEMALE											
(a) 0	20.2	60	20.1	100	60	20.5	101	60	20.6	102	60
1	21.0	60	21.1	100	55	21.6	103	60	21.6	103	60
2	21.7	60	21.3	98	55	21.4	99	60	22.0	101	60
3	22.3	60	23.1	104	55	23.3	104	60	23.4	105	59
4	23.1	59	23.5	102	55	24.4	106	60	23.3	101	59
5	23.5	59	24.3	103	55	24.7	105	60	23.9	102	59
6	23.5	59	23.8	101	55	24.7	105	60	24.1	103	59
7	24.0	59	24.0	100	55	24.3	101	60	24.4	102	59
8	24.3	59	24.9	102	55	25.8	106	60	25.5	105	59
9	25.1	59	24.5	98	55	24.9	99	60	24.6	98	59
10	25.0	59	25.1	100	55	25.6	102	60	25.7	103	59
11	27.0	59	25.7	95	55	26.4	98	60	26.1	97	59
12	26.3	59	26.3	100	55	27.1	103	60	25.8	98	59
17	27.0	59	27.8	103	55	28.4	105	59	27.9	103	59
21	28.5	59	28.2	99	55	29.1	102	59	29.0	102	59
25	28.8	59	29.1	101	55	29.9	104	59	29.9	104	59
30	29.8	57	30.2	101	55	31.6	106	59	30.8	103	59
34	31.3	57	30.8	98	55	32.7	104	59	33.1	106	59
38	32.9	56	32.4	98	54	35.6	108	59	34.2	104	59
43	34.2	56	32.8	96	54	35.2	103	59	35.8	105	59
47	36.0	56	34.9	97	54	38.2	106	59	37.0	103	59
52	38.9	56	37.0	95	54	41.0	105	59	40.6	104	58
57	40.8	46	39.2	96	44	41.5	102	50	40.1	98	48
61	40.0	45	38.2	96	44	42.4	106	50	39.7	99	48
66	--	--	--	--	--	43.8	--	50	41.4	--	47
67	41.2	45	38.9	94	44	--	--	--	--	--	--
70	40.5	45	38.3	95	43	43.5	107	48	40.1	99	46
74	39.4	44	38.5	98	43	43.5	110	46	41.0	104	43
78	42.3	43	41.0	97	42	45.5	108	46	43.0	102	41
82	44.6	42	43.1	97	39	48.0	108	45	45.3	102	40
87	43.1	41	42.6	99	38	46.7	108	43	41.1	95	33
91	41.9	39	42.5	101	35	45.2	108	40	39.0	93	31
95	41.9	38	41.8	100	32	46.2	110	35	38.8	93	24
99	42.4	35	42.9	101	30	43.1	102	30	36.6	86	21
103	42.3	31	43.1	102	27	43.2	102	25	36.1	85	18

(a) Mean body weights 2 days after first dose

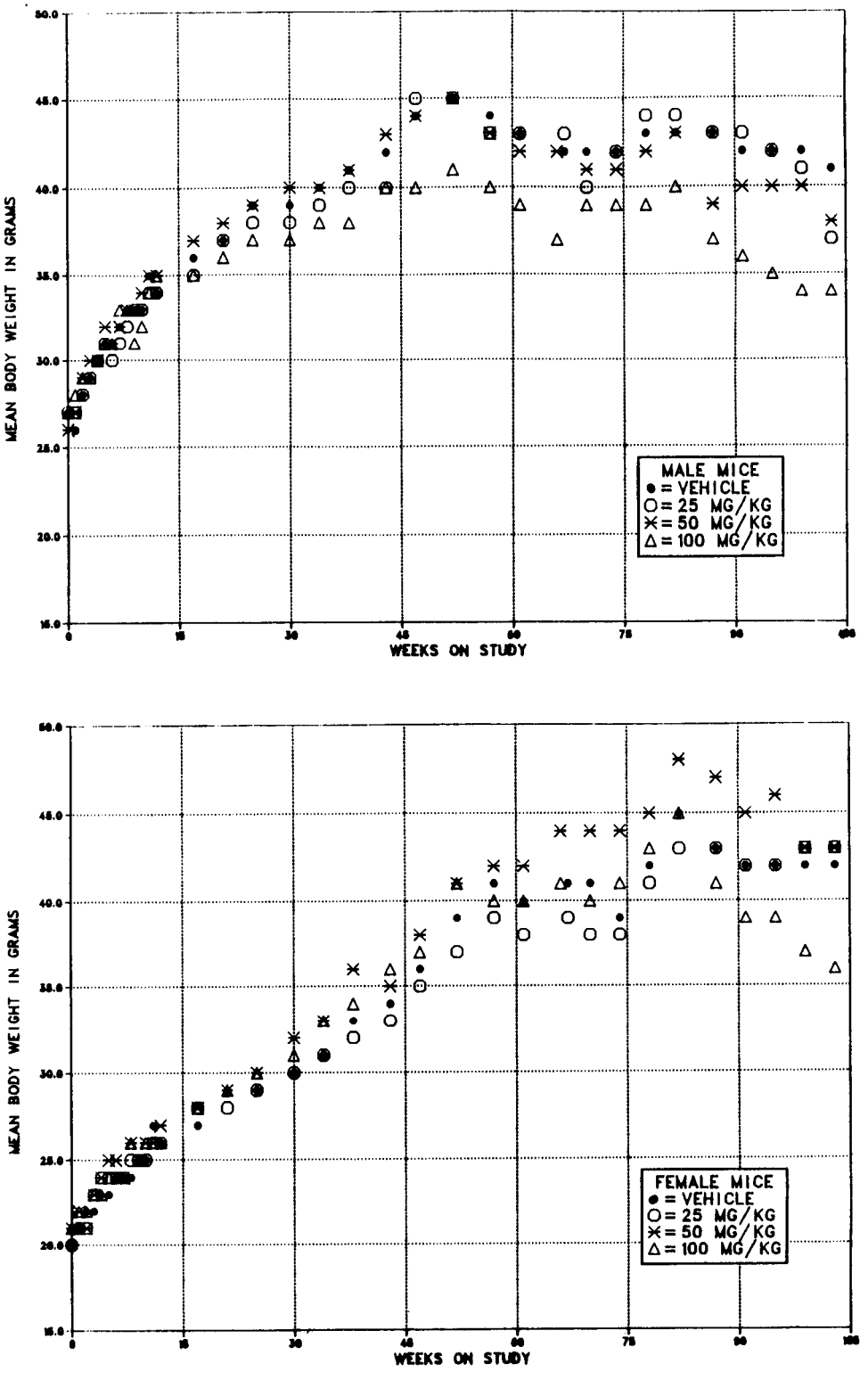


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED BENZENE IN CORN OIL FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered benzene at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 6. The survival of the high dose group of both male mice after week 96 and female mice after week 92 was significantly lower than that of the respective vehicle control groups (Table 14).

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions in the Zymbal gland, preputial gland, ovary, mammary gland, harderian gland, lung, hematopoietic system, stomach, liver, and adrenal gland. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the four groups. One vehicle control male, two low dose male, and one high dose male mice and one vehicle control female, five low dose female, and one high dose female mice that died before week 4 are not included in the statistical analyses of the results. [Because of this, some of the denominators in tumor incidence tables may be different from those in the summary appendixes.] The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 14. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	20	24	31	41
Accidentally killed (c)	2	3	1	2
Killed at termination	28	22	18	7
Died during termination period	0	1	0	0
Survival P values (d)	<0.001	0.450	0.059	<0.001
FEMALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	16	19	26	31
Accidentally killed (c)	4	5	0	1
Killed at termination	30	25	24	16
Died during termination period	0	1	0	2
Survival P values (d)	0.001	0.499	0.110	0.004

(a) Terminal kill period: week 104
(b) Includes animals killed in a moribund condition
(c) Cause of death not known
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

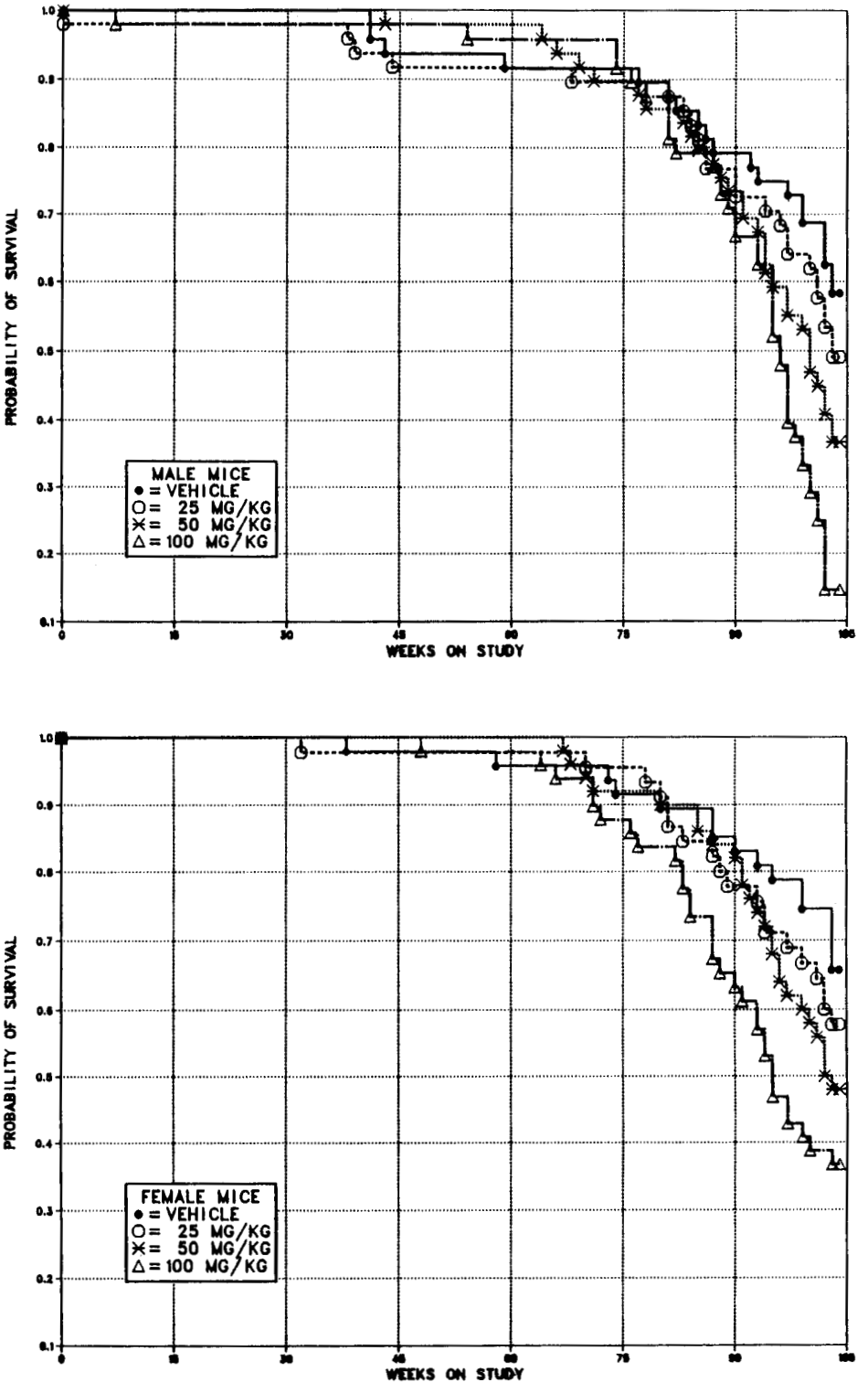


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED BENZENE IN CORN OIL FOR TWO YEARS

Zymbal Gland: Epithelial hyperplasia was observed at increased incidences in mid and high dose male and high dose female mice (Table 15). Squamous cell carcinomas in males and females occurred with positive trends. The incidences in the mid and high dose males and high dose females were significantly greater than those in the vehicle controls. All neoplasms were carcinomas; no adenomas were observed. Also, one high dose male and one high dose female had a carcinosarcoma.

The incidences of Zymbal gland carcinomas in mid dose and high dose male rats and in low dose, mid dose, and high dose female rats were greater than those in the vehicle controls (see Tables 28-30 in Discussion and Conclusions) and exceed the greatest incidences observed in corn oil vehicle historical controls (Appendix F, Table F21). The incidences of Zymbal gland carcinomas were significantly increased in mid dose and high dose male mice and in high dose female mice. In mid dose and high dose male mice and in high dose female mice, the incidences of epithelial hyperplasia of the Zymbal gland were also increased. The possible early occurrence and progression of these lesions was investigated by an examination of the Zymbal glands from the 10 animals per group killed after 12 months' exposure; no nonneoplastic or neoplastic pathologic effects were observed. One mid dose (50 mg/kg) female mouse had a small focus of acute inflammation.

TABLE 15. ANALYSIS OF ZYMBAL GLAND LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE (a)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Epithelial Hyperplasia				
Overall Rates	0/43 (0%)	3/34 (9%)	12/40 (30%)	10/39 (26%)
Squamous Cell Carcinoma (b)				
Overall Rates	0/43 (0%)	1/34 (3%)	4/40 (10%)	21/39 (54%)
Adjusted Rates	0.0%	2.9%	28.6%	87.6%
Terminal Rates	0/25 (0%)	0/15 (0%)	4/14 (29%)	5/7 (71%)
Life Table Tests	P<0.001	P=0.489	P=0.012	P<0.001
Incidental Tumor Tests	P<0.001	P=0.500	P=0.012	P<0.001
FEMALE				
Epithelial Hyperplasia				
Overall Rates	1/43 (2%)	1/32 (3%)	2/37 (5%)	6/31 (19%)
Squamous Cell Carcinoma (c)				
Overall Rates	0/43 (0%)	0/32 (0%)	1/37 (3%)	3/31 (10%)
Adjusted Rates	0.0%	0.0%	4.8%	18.8%
Terminal Rates	0/27 (0%)	0/18 (0%)	1/21 (5%)	3/16 (19%)
Life Table Tests	P=0.007	(d)	P=0.450	P=0.045
Incidental Tumor Tests	P=0.007	(d)	P=0.450	P=0.045

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Mice that died before week 4 are not included in the statistical analyses but are included in Appendixes B and D.
(b) Historical incidence at laboratory (mean): 0/100; historical incidence in NTP studies: 0/1,090
(c) Historical incidence at laboratory (mean): 0/99; historical incidence in NTP studies: 1/1,187 (<0.1%)
(d) No P values are reported because no tumors were observed in the 25 mg/kg and vehicle control groups.

Preputial Gland: Hyperplasia was observed at increased incidences in the preputial gland of low and mid dose male mice (Table 16). Squamous cell carcinomas and carcinomas (all types) occurred in male mice with positive trends. The incidences of squamous cell carcinomas in mid and high dose males and the incidences of carcinomas (all types) in mid and high dose males were greater than those of the vehicle controls. One low dose and one high dose male had a carcinosarcoma. There were no corresponding clitoral gland neoplasms in females. Epithelial hyperplasia was observed in six low dose, two mid dose, and one high dose females.

Ovary: The incidence of female mice with various nonneoplastic and neoplastic lesions in the ovary is given in Table 17. Granulosa cell tumors and benign mixed tumors occurred with significant positive trends. The incidences of granulosa cell tumors in the high dose group and benign mixed tumors in the mid and high dose groups were significantly greater than those in the vehicle controls (Table 18). The granulosa cell neoplasms consisted of well-differentiated granulosa cells arranged in tubular patterns, cell clusters separated by interconnecting strands of stromal connective tissue, or homogeneous cell populations with no definite cellular arrangement and scanty stroma. Benign mixed tumors comprised heterogeneous cell types including tubular structures arising from the ovarian surface epithelium (so-called germinal epithelium), stromal cells, and/or granulosa cells exhibiting varying degrees of luteinization. Luteomas consisted predominantly of luteinized theca and/or granulosa cells and tubular adenomas consisted of randomly arranged tubules with a low cuboidal epithelium.

TABLE 16. ANALYSIS OF PREPUTIAL GLAND LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hyperplasia (Focal, Diffuse, or Epithelial)				
Overall Rates	1/21 (5%)	18/28 (65%)	9/29 (31%)	1/35 (3%)
Squamous Cell Carcinoma				
Overall Rates	0/21 (0%)	3/28 (11%)	18/29 (62%)	28/35 (80%)
Adjusted Rates	0.0%	13.6%	80.8%	91.2%
Terminal Rates	0/13 (0%)	3/22 (14%)	14/18 (78%)	4/6 (67%)
Life Table Tests	P<0.001	P=0.225	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.225	P<0.001	P<0.001
Carcinoma, NOS				
Overall Rates	0/21 (0%)	2/28 (7%)	1/29 (3%)	3/35 (9%)
Adjusted Rates	0.0%	9.1%	4.0%	24.8%
Terminal Rates	0/13 (0%)	2/22 (9%)	0/18 (0%)	1/6 (17%)
Life Table Tests	P<0.019	P=0.359	P<0.445	P<0.043
Incidental Tumor Tests	P<0.234	P=0.359	P<0.545	P<0.234
Carcinoma (All Types) (a)				
Overall Rates	0/21 (0%)	5/28 (18%)	19/29 (66%)	31/35 (89%)
Adjusted Rates	0.0%	21.7%	81.6%	96.1%
Terminal Rates	0/13 (0%)	5/22 (22%)	14/18 (78%)	5/6 (83%)
Life Table Tests	P<0.001	P=0.091	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.091	P<0.001	P<0.001

(a) Historical incidence of adenomas or carcinomas at laboratory (mean): 0/100; historical incidence in NTP studies: 1/1,090 (<0.1%)

TABLE 17. NUMBER OF FEMALE MICE WITH OVARIAN LESIONS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

Lesion	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
No. of mice examined	47	44	49	48
Epithelial hyperplasia	12	39	31	29
Senile atrophy	15	35	32	22
Papillary cystadenoma	0	0	2	1
Luteoma	0	2	3	2
Granulosa cell tumor	1	1	6	7
Granulosa cell carcinoma	0	0	0	1
Tubular adenoma	0	0	3	3
Benign mixed tumor	0	1	12	7

TABLE 18. ANALYSIS OF OVARIAN TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (a)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Tubular Adenoma				
Overall Rates	0/47 (0%)	0/44 (0%)	3/49 (6%)	3/48 (6%)
Adjusted Rates	0.0%	0.0%	11.4%	15.8%
Terminal Rates	0/30 (0%)	0/26 (0%)	2/24 (8%)	2/18 (11%)
Life Table Tests	P=0.008	(b)	P=0.090	P=0.047
Incidental Tumor Tests	P=0.016	(b)	P=0.119	P=0.077
Granulosa Cell Tumor				
Overall Rates	1/47 (2%)	1/44 (2%)	6/49 (12%)	7/48 (15%)
Adjusted Rates	3.3%	3.8%	19.9%	28.9%
Terminal Rates	1/30 (3%)	1/26 (4%)	3/24 (13%)	4/18 (22%)
Life Table Tests	P<0.001	P=0.730	P=0.040	P=0.008
Incidental Tumor Tests	P=0.005	P=0.730	P=0.077	P=0.020
Granulosa Cell Tumor or Carcinoma (c)				
Overall Rates	1/47 (2%)	1/44 (2%)	6/49 (12%)	8/48 (17%)
Adjusted Rates	3.3%	3.8%	19.9%	31.6%
Terminal Rates	1/30 (3%)	1/26 (4%)	3/24 (13%)	4/18 (22%)
Life Table Tests	P<0.001	P=0.730	P=0.040	P=0.004
Incidental Tumor Tests	P=0.002	P=0.730	P=0.077	P=0.012
Mixed Tumor, Benign				
Overall Rates	0/47 (0%)	1/44 (2%)	12/49 (24%)	7/48 (15%)
Adjusted Rates	0.0%	3.8%	42.3%	32.9%
Terminal Rates	0/30 (0%)	1/26 (4%)	9/24 (38%)	5/18 (28%)
Life Table Tests	P<0.001	P=0.471	P<0.001	P=0.001
Incidental Tumor Tests	P<0.001	P=0.471	P<0.001	P=0.002

(a) Historical incidence of ovarian tumors at laboratory: 0/100; historical incidence in NTP studies: no more than two ovarian tumors were present in any single control group
(b) No P values are reported because no tumors were observed in the 25 mg/kg and vehicle control groups.
(c) Historical incidence in NTP studies (mean): 3/1,028 (0.3%)

Mammary Gland: Carcinomas and carcinosarcomas in female mice occurred with significant positive trends (Table 19). The incidences of carcinomas in mid and high dose female mice and of carcinosarcomas in high dose female mice were significantly greater than those in the vehicle controls. Carcinomas often showed both an organoid pattern of epithelial cell arrangement and extensive squamous differentiation. Carcinosarcomas consisted of highly anaplastic epithelial cells and a prominent spindle-cell component resembling malignant fibroblasts.

Harderian Gland: Focal hyperplasia was observed at increased incidences in dosed male and female mice (Table 20). Adenomas in males and carcinomas in females occurred with significant positive trends. The incidences of adenomas in dosed male mice were significantly greater than that in the vehicle controls. The incidence of carcinomas in high dose females was marginally greater than that in vehicle controls. These neoplasms consisted of pseudoglandular structures lined by epithelium showing loss of polarity, mild to moderate pleomorphism, and formation of multiple layers. The malignant tumors were less differentiated and were locally invasive.

Harderian glands were examined from the 10 animals per group killed at 12 months. Mild localized epithelial hyperplasia was observed in 1/10 female vehicle controls, 1/10 low dose males, and 1/10 mid dose females; this latter mouse had a small adenoma near the hyperplastic focus. One of 10 low dose females had a small focus of necrosis and acute inflammation. One mid dose male had a small adenoma.

TABLE 19. ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hyperplasia (Focal or Cystic)				
Overall Rates	2/49 (4%)	4/45 (9%)	2/50 (4%)	1/49 (2%)
Carcinoma (a)				
Overall Rates	0/49 (0%)	2/45 (4%)	5/50 (10%)	10/49 (20%)
Adjusted Rates	0.0%	6.9%	15.9%	33.2%
Terminal Rates	0/30 (0%)	0/26 (0%)	2/24 (8%)	3/18 (17%)
Life Table Tests	P<0.001	P=0.202	P=0.026	P<0.001
Incidental Tumor Tests	P<0.001	P=0.233	P=0.047	P=0.004
Carcinosarcoma				
Overall Rates	0/49 (0%)	0/45 (0%)	1/50 (2%)	4/49 (8%)
Adjusted Rates	0.0%	0.0%	2.7%	20.6%
Terminal Rates	0/30 (0%)	0/26 (0%)	0/24 (0%)	3/18 (17%)
Life Table Tests	P=0.001	(b)	P=0.495	P=0.017
Incidental Tumor Tests	P=0.003	(b)	P=0.588	P=0.030

(a) Historical incidence of carcinomas at laboratory (mean ± SD): 1/99 (1%); historical incidence in NTP studies: 15/1,187 (1% ± 2%)
(b) No P values are reported because no tumors were observed in the 25 mg/kg and vehicle control groups.

TABLE 20. ANALYSIS OF HARDERIAN GLAND LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Focal Hyperplasia				
Overall Rates	0/49 (0%)	5/46 (11%)	11/49 (22%)	7/48 (15%)
Adenoma (a)				
Overall Rates	0/49 (0%)	9/46 (20%)	13/49 (27%)	11/48 (23%)
Adjusted Rates	0.0%	33.2%	51.7%	56.2%
Terminal Rates	0/28 (0%)	6/22 (27%)	8/18 (44%)	2/7 (29%)
Life Table Tests	P<0.001	P=0.001	P<0.001	P<0.001
Incidental Tumor Tests	P=0.001	P=0.001	P<0.001	P=0.003
Carcinoma				
Overall Rates	1/49 (2%)	2/46 (4%)	0/49 (0%)	3/48 (6%)
Adjusted Rates	3.6%	8.2%	0.0%	11.7%
Terminal Rates	1/28 (4%)	1/22 (5%)	0/18 (0%)	0/7 (0%)
Life Table Tests	P=0.064	P=0.423	P=0.588N	P=0.128
Incidental Tumor Tests	P=0.309	P=0.467	P=0.588N	P=0.408
Adenoma or Carcinoma				
Overall Rates	1/49 (2%)	10/46 (22%)	13/49 (26%)	14/48 (29%)
Adjusted Rates	3.6%	35.8%	51.7%	61.3%
Terminal Rates	1/28 (4%)	6/22 (27%)	8/18 (44%)	2/7 (29%)
Life Table Tests	P<0.001	P=0.002	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P=0.003	P<0.001	P=0.002
FEMALE				
Focal or Diffuse Hyperplasia				
Overall Rates	6/48 (13%)	10/44 (23%)	11/50 (22%)	10/47 (21%)
Adenoma (b)				
Overall Rates	5/48 (10%)	6/44 (14%)	10/50 (20%)	6/47 (13%)
Adjusted Rates	16.7%	24.0%	27.4%	27.1%
Terminal Rates	5/30 (17%)	6/25 (24%)	2/24 (8%)	4/18 (22%)
Life Table Tests	P=0.133	P=0.369	P=0.090	P=0.204
Incidental Tumor Tests	P=0.311	P=0.369	P=0.209	P=0.281
Carcinoma				
Overall Rates	0/48 (0%)	0/44 (0%)	0/50 (0%)	4/47 (9%)
Adjusted Rates	0.0%	0.0%	0.0%	17.8%
Terminal Rates	0/30 (0%)	0/25 (0%)	0/24 (0%)	1/18 (6%)
Life Table Tests	P<0.001	(c)	(c)	P=0.020
Incidental Tumor Tests	P=0.003	(c)	(c)	P=0.060
Adenoma or Carcinoma				
Overall Rates	5/48 (10%)	6/44 (14%)	10/50 (20%)	10/47 (21%)
Adjusted Rates	16.7%	24.0%	27.4%	41.1%
Terminal Rates	5/30 (17%)	6/25 (24%)	2/24 (8%)	5/18 (28%)
Life Table Tests	P=0.009	P=0.369	P=0.090	P=0.017
Incidental Tumor Tests	P=0.046	P=0.369	P=0.209	P=0.049

(a) Historical incidence at laboratory (mean ± SD): 1/100 (1%); historical incidence in NTP studies: 32/1,090 (3% ± 3%)
(b) Historical incidence at laboratory (mean ± SD): 0/99; historical incidence in NTP studies: 11/1,187 (0.9% ± 1%)
(c) No P values are reported because no tumors were observed in the 25 mg/kg or 50 mg/kg and vehicle control groups.

Lung: The incidences of alveolar epithelial hyperplasia and alveolar/bronchiolar neoplasms were increased in dosed male and female mice (Table 21). Most of the significant increases were due to carcinomas. For male mice, the life table and incidental tumor tests give different results regarding the statistical significance of dose-response trends and of increased tumor incidences in the mid and high dose groups. In this instance, the life table test should be given the greater emphasis, since (1) the increased incidence of lung tumors is due primarily to malignant, potentially life-threatening tumors, (2) the incidental tumor test has somewhat reduced sensitivity because of the excessive mortality in the high dose group, and (3) the unadjusted analyses (see Appendix E, Table E3) indicate a significant increase in tumor incidence, despite the reduced survival in the high dose group.

TABLE 21. ANALYSIS OF LUNG LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Alveolar Epithelial Hyperplasia				
Overall Rates	2/49 (4%)	3/48 (6%)	7/50 (14%)	10/49 (20%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	6/49 (12%)	6/48 (13%)	8/50 (16%)	12/49 (24%)
Adjusted Rates	18.9%	21.1%	29.3%	41.5%
Terminal Rates	4/28 (14%)	3/23 (13%)	2/18 (11%)	0/7 (0%)
Life Table Tests	P<0.001	P=0.499	P=0.188	P=0.005
Incidental Tumor Tests	P=0.179	P=0.609	P=0.486	P=0.326
Alveolar/Bronchiolar Carcinoma				
Overall Rates	5/49 (10%)	11/48 (23%)	12/50 (24%)	14/49 (29%)
Adjusted Rates	15.6%	36.3%	41.9%	58.8%
Terminal Rates	3/28 (11%)	6/23 (26%)	5/18 (28%)	2/7 (29%)
Life Table Tests	P<0.001	P=0.052	P=0.017	P<0.001
Incidental Tumor Tests	P=0.046	P=0.083	P=0.083	P=0.073
Alveolar/Bronchiolar Adenoma or Carcinoma (a)				
Overall Rates	10/49 (20%)	16/48 (33%)	19/50 (38%)	21/49 (43%)
Adjusted Rates	29.8%	49.1%	60.0%	71.1%
Terminal Rates	6/28 (21%)	8/23 (35%)	7/18 (39%)	2/7 (29%)
Life Table Tests	P<0.001	P=0.069	P=0.007	P<0.001
Incidental Tumor Tests	P=0.056	P=0.124	P=0.070	P=0.094
FEMALE				
Alveolar Epithelial Hyperplasia				
Overall Rates	1/49 (2%)	1/42 (2%)	9/50 (18%)	6/49 (12%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	4/49 (8%)	2/42 (5%)	5/50 (10%)	9/49 (18%)
Adjusted Rates	13.3%	7.2%	15.7%	44.0%
Terminal Rates	4/30 (13%)	1/24 (4%)	2/24 (8%)	7/18 (39%)
Life Table Tests	P=0.003	P=0.437N	P=0.398	P=0.011
Incidental Tumor Tests	P=0.010	P=0.435N	P=0.514	P=0.020
Alveolar/Bronchiolar Carcinoma				
Overall Rates	0/49 (0%)	3/42 (7%)	6/50 (12%)	6/49 (12%)
Adjusted Rates	0.0%	12.5%	22.8%	27.0%
Terminal Rates	0/30 (0%)	3/24 (13%)	5/24 (21%)	4/18 (22%)
Life Table Tests	P=0.002	P=0.084	P=0.010	P=0.004
Incidental Tumor Tests	P=0.006	P=0.084	P=0.013	P=0.009
Alveolar/Bronchiolar Adenoma or Carcinoma (b)				
Overall Rates	4/49 (8%)	5/42 (12%)	10/50 (20%)	13/49 (27%)
Adjusted Rates	13.3%	19.3%	32.7%	57.1%
Terminal Rates	4/30 (13%)	4/24 (17%)	6/24 (25%)	9/18 (50%)
Life Table Tests	P<0.001	P=0.366	P=0.039	P<0.001
Incidental Tumor Tests	P<0.001	P=0.368	P=0.071	P=0.002

(a) Historical incidence at laboratory (mean ± SD): 14/100 (14%); historical incidence in NTP studies: 155/1,082 (14% ± 6%)
(b) Historical incidence at laboratory (mean ± SD): 4/97 (4%); historical incidence in NTP studies: 52/1,103 (5% ± 4%)

Hematopoietic System: Hematopoietic hyperplasia was observed at increased incidences in the bone marrow of dosed mice of each sex (Table 22). Splenic hematopoiesis was also increased with dose (male: vehicle control, 5/49; low dose, 9/48; mid dose; 19/49; high dose, 24/47; female: 9/49; 10/45; 6/50; 14/49). Neoplasms diagnosed as leukemia were considered by the Pathology Working Group to be malignant lymphomas with associated "leukemia" (i.e., evidence of elevated lymphocytes/lymphoblasts in peripheral blood). Thus, the lymphoma or leukemia data given below should be viewed as all lymphoma for evaluation purposes. Malignant lymphomas in male and female mice occurred with significant positive trends. The incidences of malignant lymphomas in all dosed groups of males and females were significantly greater than those in the vehicle controls by the life table test, which is generally regarded as the more appropriate method of statistical analysis for these potentially life-threatening neoplasms.

TABLE 22. ANALYSIS OF HEMATOPOIETIC SYSTEM LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Hematopoietic Hyperplasia (Bone Marrow)				
Overall Rates	0/49 (0%)	11/48 (22%)	10/50 (20%)	25/49 (50%)
Lymphoma, All Malignant				
Overall Rates	4/49 (8%)	9/48 (19%)	9/50 (18%)	15/49 (31%)
Adjusted Rates	12.4%	31.3%	42.2%	69.3%
Terminal Rates	2/28 (7%)	5/23 (22%)	7/18 (39%)	3/7 (43%)
Life Table Tests	P<0.001	P=0.075	P=0.030	P<0.001
Incidental Tumor Tests	P=0.003	P=0.116	P=0.072	P=0.022
Leukemia				
Overall Rates	0/49 (0%)	1/48 (2%)	1/50 (2%)	0/49 (0%)
Lymphoma or Leukemia (a)				
Overall Rates	4/49 (8%)	10/48 (21%)	10/50 (20%)	15/49 (31%)
Adjusted Rates	12.4%	33.1%	44.0%	69.3%
Terminal Rates	2/28 (7%)	5/23 (22%)	7/18 (39%)	3/7 (43%)
Life Table Tests	P<0.001	P=0.048	P=0.018	P<0.001
Incidental Tumor Tests	P=0.006	P=0.080	P=0.052	P=0.022
FEMALE				
Hematopoietic Hyperplasia (Bone Marrow)				
Overall Rates	3/49 (6%)	14/45 (31%)	8/50 (16%)	13/49 (26%)
Lymphoma, All Malignant				
Overall Rates	15/49 (31%)	24/45 (53%)	24/50 (48%)	20/49 (41%)
Adjusted Rates	41.7%	68.0%	62.5%	53.6%
Terminal Rates	10/30 (33%)	15/26 (58%)	11/24 (46%)	5/18 (28%)
Life Table Tests	P=0.031	P=0.021	P=0.025	P=0.037
Incidental Tumor Tests	P=0.446	P=0.028	P=0.109	P=0.357
Leukemia				
Overall Rates	0/49 (0%)	1/45 (2%)	2/50 (4%)	2/49 (4%)
Lymphoma or Leukemia (b)				
Overall Rates	15/49 (31%)	25/45 (56%)	26/50 (52%)	22/49 (45%)
Adjusted Rates	41.7%	68.7%	64.6%	56.2%
Terminal Rates	10/30 (33%)	15/26 (58%)	11/24 (46%)	5/18 (28%)
Life Table Tests	P=0.014	P=0.014	P=0.012	P=0.017
Incidental Tumor Tests	P=0.309	P=0.014	P=0.061	P=0.272

(a) Historical incidence at laboratory (mean ± SD): 13/100 (13%); historical incidence in NTP studies: 132/1,090 (12% ± 6%)
(b) Historical incidence at laboratory (mean ± SD): 25/99 (25%); historical incidence in NTP studies: 258/1,187 (22% ± 9%)

Forestomach: Epithelial hyperplasia and hyperkeratosis were observed at increased incidences in low dose males and mid dose and high dose females (Table 23). Squamous cell papillomas in male mice occurred with a significant positive trend. The combined incidence in male mice with either squamous cell papillomas or carcinomas, however, did not occur with a significant trend by the incidental tumor test even though the number of neoplasms in vehicle controls remained the same (2/45) and the number in the dosed groups increased (from 8/124 to 10/124). The increased incidences of squamous cell papillomas and squamous cell papillomas or carcinomas (combined) in high dose male mice were not statistically significant by the incidental tumor test. The increased incidences of squamous cell papillomas in dosed females were also not significant; no squamous cell carcinomas were observed.

TABLE 23. ANALYSIS OF FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Epithelial Hyperplasia				
Overall Rates	1/45 (2%)	11/42 (26%)	2/44 (5%)	0/38 (0%)
Hyperkeratosis				
Overall Rates	1/45 (2%)	7/42 (17%)	4/44 (9%)	1/38 (3%)
Squamous Cell Papilloma				
Overall Rates	2/45 (4%)	1/42 (2%)	2/44 (5%)	5/38 (13%)
Adjusted Rates	6.8%	4.3%	8.7%	38.5%
Terminal Rates	1/28 (4%)	1/23 (4%)	1/18 (6%)	2/7 (29%)
Life Table Tests	P=0.003	P=0.567N	P=0.556	P=0.014
Incidental Tumor Tests	P=0.048	P=0.546N	P=0.685	P=0.161
Squamous Cell Carcinoma				
Overall Rates	0/45 (0%)	1/42 (2%)	1/44 (2%)	1/38 (3%)
Squamous Cell Papilloma or Carcinoma (a)				
Overall Rates	2/45 (4%)	2/42 (5%)	3/44 (7%)	5/38 (13%)
Adjusted Rates	6.8%	8.7%	13.3%	38.5%
Terminal Rates	1/28 (4%)	2/23 (9%)	1/18 (6%)	2/7 (29%)
Life Table Tests	P=0.004	P=0.623	P=0.335	P=0.014
Incidental Tumor Tests	P=0.074	P=0.640	P=0.521	P=0.161
FEMALE				
Epithelial Hyperplasia				
Overall Rates	1/42 (2%)	3/40 (8%)	6/45 (13%)	6/42 (14%)
Hyperkeratosis				
Overall Rates	0/42 (0%)	1/40 (2%)	5/45 (11%)	9/42 (19%)
Squamous Cell Papilloma (b)				
Overall Rates	1/42 (2%)	3/40 (7%)	6/45 (13%)	5/42 (12%)
Adjusted Rates	2.3%	8.6%	23.7%	25.1%
Terminal Rates	0/29 (0%)	1/26 (4%)	5/24 (21%)	4/18 (22%)
Life Table Tests	P=0.022	P=0.288	P=0.038	P=0.040
Incidental Tumor Tests	P=0.071	P=0.134	P=0.059	P=0.079

(a) Historical incidence at laboratory (mean): 0/100; historical incidence in NTP studies: 7/1,055 (0.7%)
(b) Historical incidence at laboratory (mean): 0/99; historical incidence in NTP studies: 7/1,077 (0.6%)

Liver: In female mice, the incidences of hepatocellular adenomas in the low dose group and hepatocellular adenomas or carcinomas (combined) in the low and mid dose groups were significantly greater than those in the vehicle controls (Table 24).

Adrenal Gland: The incidences of hyperplasia in the adrenal capsule in dosed mice of each sex (except high dose males) were greater than those in the vehicle controls (Table 25). The incidence of pheochromocytomas in mid dose male mice was significantly greater than that in the vehicle controls. In female mice, pheochromocytomas or malignant pheochromocytomas (combined) occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls.

TABLE 24. ANALYSIS OF LIVER TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Hepatocellular Adenoma				
Overall Rates	7/49 (14%)	11/48 (23%)	6/50 (12%)	3/47 (6%)
Adjusted Rates	25.0%	40.4%	25.4%	14.5%
Terminal Rates	7/28 (25%)	8/23 (35%)	3/18 (17%)	0/7 (0%)
Life Table Tests	P=0.519	P=0.108	P=0.438	P=0.518
Incidental Tumor Tests	P=0.221N	P=0.131	P=0.583	P=0.519N
Hepatocellular Carcinoma				
Overall Rates	9/49 (18%)	8/48 (17%)	17/50 (34%)	8/47 (17%)
Adjusted Rates	22.0%	27.8%	49.4%	46.7%
Terminal Rates	1/28 (4%)	4/23 (17%)	3/18 (17%)	2/7 (29%)
Life Table Tests	P=0.072	P=0.589	P=0.028	P=0.293
Incidental Tumor Tests	P=0.234N	P=0.392N	P=0.231	P=0.215N
Hepatocellular Adenoma or Carcinoma (a)				
Overall Rates	15/49 (31%)	17/48 (35%)	22/50 (44%)	11/47 (23%)
Adjusted Rates	39.3%	54.9%	62.7%	54.8%
Terminal Rates	7/28 (25%)	10/23 (43%)	6/18 (33%)	2/7 (29%)
Life Table Tests	P=0.076	P=0.256	P=0.029	P=0.225
Incidental Tumor Tests	P=0.136N	P=0.423	P=0.238	P=0.207N
FEMALE				
Hepatocellular Adenoma				
Overall Rates	1/49 (2%)	8/44 (18%)	5/50 (10%)	4/49 (8%)
Adjusted Rates	3.3%	30.8%	15.6%	17.4%
Terminal Rates	1/30 (3%)	8/26 (31%)	1/24 (4%)	2/18 (11%)
Life Table Tests	P=0.156	P=0.008	P=0.079	P=0.077
Incidental Tumor Tests	P=0.289	P=0.008	P=0.168	P=0.124
Hepatocellular Carcinoma				
Overall Rates	3/49 (6%)	4/44 (9%)	8/50 (16%)	4/49 (8%)
Adjusted Rates	9.1%	11.9%	28.0%	17.0%
Terminal Rates	2/30 (7%)	1/26 (4%)	5/24 (21%)	1/18 (6%)
Life Table Tests	P=0.169	P=0.440	P=0.058	P=0.278
Incidental Tumor Tests	P=0.401	P=0.498	P=0.101	P=0.471
Hepatocellular Adenoma or Carcinoma (b)				
Overall Rates	4/49 (8%)	12/44 (27%)	13/50 (26%)	7/49 (14%)
Adjusted Rates	12.3%	40.1%	39.9%	27.5%
Terminal Rates	3/30 (10%)	9/26 (35%)	6/24 (25%)	2/18 (11%)
Life Table Tests	P=0.103	P=0.014	P=0.008	P=0.086
Incidental Tumor Tests	P=0.339	P=0.017	P=0.026	P=0.209

(a) Historical incidence at laboratory (mean ± SD): 35/100 (35%); historical incidence in NTP studies: 340/1,084 (31% ± 10%)
(b) Historical incidence at laboratory (mean ± SD): 6/98 (6%); historical incidence in NTP studies: 80/1,176 (7% ± 3%)

TABLE 25. ANALYSIS OF ADRENAL GLAND LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
MALE				
Hyperplasia (Adrenal Capsule)				
Overall Rates	2/47 (4%)	32/48 (67%)	14/49 (29%)	4/46 (9%)
Pheochromocytoma				
Overall Rates	1/47 (2%)	1/48 (2%)	7/49 (14%)	1/46 (2%)
Adjusted Rates	2.9%	4.3%	30.0%	4.3%
Terminal Rates	0/27 (0%)	1/23 (4%)	3/18 (17%)	0/6 (0%)
Life Table Tests	P=0.096	P=0.725	P=0.010	P=0.632
Incidental Tumor Tests	P=0.540	P=0.757N	P=0.045	P=0.529N
FEMALE				
Hyperplasia (Adrenal Capsule)				
Overall Rates	5/49 (10%)	19/44 (43%)	34/50 (68%)	30/48 (63%)
Pheochromocytoma				
Overall Rates	6/49 (12%)	1/44 (2%)	1/50 (2%)	1/48 (2%)
Adjusted Rates	20.0%	3.8%	4.2%	5.9%
Terminal Rates	6/30 (20%)	1/26 (4%)	1/24 (4%)	1/17 (6%)
Life Table Tests	P=0.097N	P=0.080N	P=0.097N	P=0.192N
Incidental Tumor Tests	P=0.097N	P=0.080N	P=0.097N	P=0.192N
Pheochromocytoma, Malignant				
Overall Rates	2/49 (4%)	0/44 (0%)	0/50 (0%)	0/48 (0%)
Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates	8/49 (16%)	1/44 (2%)	1/50 (2%)	1/48 (2%)
Adjusted Rates	23.9%	3.8%	4.2%	5.9%
Terminal Rates	6/30 (20%)	1/26 (4%)	1/24 (4%)	1/17 (6%)
Life Table Tests	P=0.030N	P=0.030N	P=0.035N	P=0.085N
Incidental Tumor Tests	P=0.018N	P=0.033N	P=0.025N	P=0.046N

Hematologic Analyses

Hematologic effects were limited to lymphocytopenia. For both males and females, the analyses of variance (Appendix N, Table N8) suggest strong, temporally variable dose effects in the second year of the studies (group B). Significant dose effects are also evident for males in the first year. Figure 7 and Table N8 show the temporal variation in dose response in males to be mainly the result of time-oriented changes in the magnitude of difference between vehicle control and dosed groups. However, with the exception of month 12 (group C), there is consistent evidence of compound-related depression in lymphocytes in months 3 through 21, suggesting a compound effect in males. A higher degree of temporal variability in pattern of response makes a similar effect in females questionable.

The NTP (Appendix G) found that benzene administered by gavage induced micronuclei in male and female B6C3F$_1$ mice; males were more sensitive than females (Choy et al., 1985).

A complete statistical analysis of all hematology data is available from the National Toxicology Program. The technical quality of certain of these data was questionable; thus, more detailed analyses (e.g., investigation of the association between hematologic and pathologic changes) are deemed inappropriate for these data.

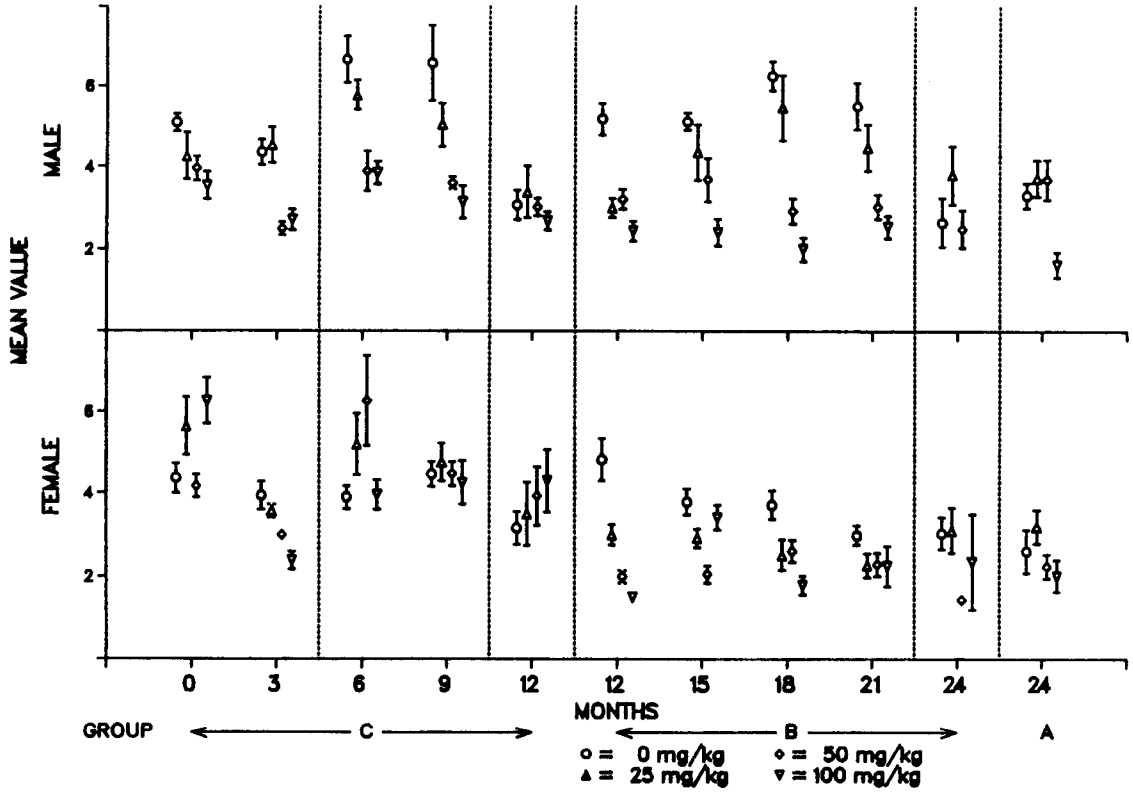


FIGURE 7. RESULTS OF LYMPHOCYTE DETERMINATIONS IN MICE IN THE TWELVE- AND TWENTY-FOUR-MONTH GAVAGE STUDIES OF BENZENE

IV. DISCUSSION AND CONCLUSIONS

DESIGN
BODY WEIGHTS AND SURVIVAL
HEMATOLOGY
PATHOLOGY
METABOLISM AND METABOLITES
GENETIC TOXICOLOGY
INITIATED EXPERIMENTS
CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

DESIGN

Two-year toxicology and carcinogenicity studies of benzene (99.7% pure) were conducted on groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex. Doses of 0, 50, 100, or 200 mg/kg benzene were administered to male rats by gavage in corn oil, 5 days per week for 103 weeks. Doses of 0, 25, 50, or 100 mg/kg were administered to female rats and mice of each sex on the same schedule. Doses for the 2-year studies were selected after evaluation of 17-week studies in which groups of 10 or 15 rats and 10 or 15 mice of each sex were administered 0, 25, 50, 100, 200, 400, or 600 mg/kg. The only clinical signs recorded for these 3-month studies were lowered body weights and ocular discharge in rats and tremors in mice in the higher dosed groups; some lymphoid depletion was observed in rats and leukopenia in mice.

BODY WEIGHTS AND SURVIAL

Mean body weights of some groups of dosed rats and mice were lower than those of the vehicle controls, and survival of some dosed groups was significantly lower than that of the corresponding vehicle controls. For male rats, the mean body weights after week 22 decreased with dose. The mean body weights of the high dose male rats were notably lower than those of the vehicle controls, and mean body weights of mid and high dose male rats were slightly lower than those of the vehicle controls (see Table 5 and Figure 2). Mean body weights of female rats were slightly lower than those of the vehicle controls after week 62.

Survival decreased with increasing dose for both male and female rats (Table 26). Survival of the high dose male rats and of the mid and high dose female rats was significantly lower than that of the vehicle controls; survival in all groups of rats, except high dose male rats, was 50% or more at 104 weeks. The reduced survival observed for the high dose group of male rats (16/50, 32%) reflects to some degree a likely toxic response from the 200 mg/kg dose regimen, double the high dose used for the female rats and male and female mice (100 mg/kg). A partial reason for the apparent decrease in survival in dosed female rats is the greater than average survival seen for the vehicle controls (46/50, 92%). Except for the survival of high dose females (25/50, 50%), the numbers of animals alive at the end of the study for the low dose (38/50, 76%) and the mid dose (34/50, 68%) groups are considered to be good. In any event, survival at week 92 of all groups was 60% or more. Most rats that died early had neoplasia.

TABLE 26. SURVIVAL OF F344/N RATS AND B6C3F$_1$ MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Week	Vehicle Control	Low Dose	Mid Dose	High Dose
RATS					
Male					
	92	35/50 (70%)	38/50 (76%)	31/50 (62%)	30/50 (60%)
	104	32/50 (64%)	29/50 (58%)	25/50 (50%)	(a) 16/50 (32%)
Female					
	92	49/50 (98%)	42/50 (84%)	40/50 (80%)	38/50 (76%)
	104	46/50 (92%)	38/50 (76%)	(a) 34/50 (68%)	(a) 25/50 (50%)
MICE					
Male					
	91	38/50 (76%)	34/50 (68%)	35/50 (70%)	32/50 (64%)
	104	28/50 (56%)	23/50 (46%)	18/50 (36%)	(a) 7/50 (14%)
Female					
	91	39/50 (78%)	35/50 (70%)	40/50 (80%)	31/50 (62%)
	104	30/50 (60%)	26/50 (52%)	24/50 (48%)	(a) 18/50 (36%)

(a) Decreased ($P<0.05$) survival compared with vehicle controls

Mean body weights of mid and high dose male mice and high dose female mice were lower than those of the vehicle controls. Survival of high dose male and female mice was significantly lower than that of the vehicle controls (see Table 26). The lower survival of the dosed groups of mice may have been a consequence of the increased incidences of life-threatening lymphomas and alveolar/bronchiolar carcinomas in the dosed groups rather than a singular toxic effect of benzene. At week 92 (see Table 26), for instance, survival of all groups of mice was above 60%.

HEMATOLOGY

Epidemiologic studies have shown that exposure of workers to benzene is associated with increased risk of aplastic anemia and of leukemia (IARC, 1982; Infante, 1978; Infante and White, 1983; Grossenbacher and Lob, 1982; Decoufle et al., 1983; Aksoy, 1985; Infante and White, 1985; Rinsky et al., 1986). Benzene-associated leukopenia has been reported in humans, AKR/S mice, CD mice, and Wistar rats.

The number of blood lymphocytes per cubic millimeter in C57BL/6 BNL mice exposed to benzene at 100 or 400 ppm by inhalation for 6 hours per day, 5 days a week for 2 weeks, was 40%-50% that of the controls. The number of blood lymphocytes was lower than that of the controls after 4, 8, or 16 weeks' exposure at 300 ppm but returned to control levels 8-10 weeks after termination of exposure (Cronkite et al., 1985).

Benzene affected the hematopoietic system of F344/N rats and B6C3F$_1$ mice in the current 17-week studies; dose-related leukopenia, predominately a lymphocytopenia, was observed for rats and mice of each sex, and compound-related lymphoid depletion and increased extramedullary hematopoiesis in the spleen were observed in rats of each sex.

Reportable hematologic data, as well as the blood collection techniques and attendant problems together with the conclusions reached for the 2-year studies, are recorded in Appendix N. Any interpretation of the hematologic data from these studies should be made with appropriate caution, since several variables were outside their appropriate range during the course of these investigations and in several instances, atypical vehicle control group values were obtained. In the opinion of NTP, hematologic effects considered reasonably interpretable are limited to lymphocytopenia and associated leukocytopenia in benzene-exposed rats and mice. Attempts to correlate hematologic changes with pathologic changes would not be appropriate, since the quality of the large amounts of hematologic data that were generated remains questionable. Those indexes that deserve reporting are described below.

For the 2-year studies, leukopenia was observed in dosed male rats during the early part of the study, and values returned near control levels at the 21-month collection (Appendix N). In dosed female rats, leukopenia was evident between the 3rd and 12th months. In male vehicle control mice, the white blood cell counts were greater than expected at the 6- and 9-month collections and could give a misimpression of the compound-related leukopenia; similarly, high vehicle control group values for males were noted at 18 and 21 months. In dosed female mice, benzene-related leukopenia was observed at 12 and 18 months and lends support to the possibility that the decreases seen in the male mice might have been associated with benzene administration as well.

A dose-related lymphocytopenia was evident in male rats from 3 to 21 months (Appendix N). A similar, yet lesser effect was seen in female rats. For male mice, a decrease in lymphocytes was seen at the 3- through 9-month interval (Group C) and during the 12- through 21-month period (Group B). The lymphocytopenia was evident for female mice between 12 and 18 months.

Thus, exposure of rats and mice to benzene in these studies produced a mild to moderate leukocytopenia/lymphocytopenia. How this effect influences the other observed toxic and pathologic responses remains unknown.

PATHOLOGY

Increased incidences of neoplasms were observed at multiple sites for male rats, female rats, male mice, and female mice (Tables 27-29).

TABLE 27. INCIDENCES OF SELECTED NONNEOPLASTIC OR NEOPLASTIC LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Rats								Mice							
	Male				Female				Male				Female			
	Veh Cont	Low Dose	Mid Dose	High Dose	Veh Cont	Low Dose	Mid Dose	High Dose	Veh Cont	Low Dose	Mid Dose	High Dose	Veh Cont	Low Dose	Mid Dose	High Dose
Zymbal Gland																
Hyperplasia	0/32	6/46	2/42	3/42	0/45	0/40	6/44	1/46	0/43	3/34	12/40	10/39	1/43	1/32	2/37	6/31
Carcinoma	2/32	6/46	10/42	17/42	0/45	5/40	5/44	14/46	0/43	1/34	4/40	21/39	0/43	0/32	1/37	3/31
Hematopoietic System																
Spleen, lymphoid depletion	0/49	19/48	8/47	23/47	0/50	11/50	8/49	10/49								
Bone marrow, hyperplasia									0/49	11/48	10/50	25/49	3/49	14/45	8/50	13/49
Malignant lymphoma									4/49	9/48	9/50	15/49	15/49	24/45	24/50	20/49
Forestomach																
Hyperkeratosis	2/48	4/44	3/48	9/47					1/45	7/42	4/44	0/38	0/42	1/40	5/45	7/42
Acanthosis	2/48	4/44	3/48	10/47												
Squamous cell papilloma									2/45	1/42	2/44	5/38	1/42	3/40	6/45	5/42
Squamous cell carcinoma									0/45	1/42	1/44	1/38				
Adrenal Gland																
Zona fasciculata (focal hyperplasia)	0/50	13/49	0/48	2/49	0/50	15/50	0/47	0/49								
Hyperplasia of capsule									2/47	32/48	14/49	4/46	5/49	19/44	34/50	30/48
Pheochromocytoma									1/47	1/48	7/49	1/46	6/49	1/44	1/50	1/48
Oral Cavity																
Squamous cell papilloma or carcinoma	1/50	9/50	16/50	19/50	1/50	5/50	12/50	9/50								
Lung																
Alveolar hyperplasia									2/49	3/48	7/50	10/49	1/49	1/42	9/50	6/49
A/B adenoma									6/49	6/48	8/50	12/49	4/49	2/42	5/50	9/49
A/B carcinoma									5/49	11/48	12/50	14/49	0/49	3/42	6/50	6/49
A/B adenoma or carcinoma									10/49	16/48	19/50	21/49	4/49	5/42	10/50	13/49
Skin																
Squamous cell papilloma or carcinoma	0/50	7/50	4/50	11/50												
Liver																
Adenoma	2/50	2/48	4/49	1/49	0/50	3/49	1/50	0/50	7/49	11/48	6/50	3/47	1/49	8/44	5/50	4/49
Adenoma or carcinoma	2/50	2/48	5/49	1/49					15/49	17/48	22/50	11/47	4/49	12/44	13/50	7/49
Harderian Gland																
Focal hyperplasia									0/49	5/46	11/49	7/48	5/48	10/44	11/50	9/47
Adenoma									0/49	9/46	13/49	11/48	5/48	6/44	10/50	6/47
Adenoma or carcinoma									1/49	10/46	13/49	14/48	5/48	6/44	10/50	10/47
Preputial Gland																
Hyperplasia									1/21	18/28	9/29	1/35				
Carcinomas									0/21	5/28	19/29	31/35				
Ovary																
Granulosa cell tumor													1/47	1/44	6/49	7/48
Benign mixed tumor													0/47	1/44	12/49	7/48
Tubular adenoma													0/47	1/44	3/49	3/48
Mammary Gland																
Carcinoma													0/49	2/45	5/50	10/49
Carcinosarcoma													0/49	0/45	1/50	4/49

TABLE 28. PRIMARY NEOPLASMS IN F344/N RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

Site	Vehicle Control	Low Dose	Mid Dose	High Dose
		(percent of neoplasm-bearing animals)		
MALE				
Oral cavity	(a) 2	(b) 18	(b) 32	(b) 38
Zymbal gland	(a) 6	15	(b) 24	(b) 43
Skin	(a) 2	(c) 14	(c) 10	(b) 24
FEMALE				
Oral cavity	(a) 2	(c) 10	(b) 24	(b) 18
Zymbal gland	(a) 0	(b) 13	(b) 14	(b) 33
Uterus	(a) 14	14	14	(b) 28

(a) Dose-related trend ($P<0.05$)
(b) Increased ($P<0.05$) relative to vehicle controls
(c) Marginal increase ($P<0.10$) relative to vehicle controls

TABLE 29. PRIMARY NEOPLASMS IN B6C3F$_1$ MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

Site	Vehicle Control	Low Dose	Mid Dose	High Dose
		(percent of neoplasm-bearing animals)		
MALE				
Zymbal gland	(a) 0	3	(b) 10	(b) 54
Preputial gland	(a) 0	(c) 18	(b) 66	(b) 89
Harderian gland	(a) 2	(b) 22	(b) 27	(b) 29
Lung	(a) 20	33	(b) 38	(b) 43
Lymphoma/leukemia	(a) 8	(b) 21	(b) 20	(b) 31
Liver	31	35	44	23
FEMALE				
Zymbal gland	(a) 0	0	3	(b) 10
Ovary	(a) 2	9	(b) 49	(b) 40
Mammary gland	(a) 0	4	(b) 12	(b) 28
Harderian gland	(a) 10	14	20	(b) 21
Lung	(a) 8	12	(c) 20	(b) 27
Lymphoma/leukemia	(a) 31	(b) 56	(b) 52	(b) 45
Liver	8	(b) 27	(b) 26	14

(a) Dose-related trend ($P<0.05$)
(b) Increased ($P<0.05$) relative to vehicle controls
(c) Marginal increase ($P<0.10$) relative to vehicle controls

Compound-related effects on the hematopoietic system, Zymbal gland, forestomach, and adrenal glands were found for both rats and mice. The oral cavity was affected in rats only; and the lung, liver, harderian gland, preputial gland, ovary, and mammary gland were affected in mice only.

Hematopoietic System: As was seen in the 17-week studies, lymphoid depletion of the spleen was observed at increased incidences in dosed male and female rats (see Table 27); lymphoid depletion of the thymus was seen in dosed male rats. Bone marrow hematopoietic hyperplasia was observed at increased incidences in dosed mice of each sex.

The incidences of malignant lymphomas in all dose groups of mice were greater than those of the vehicle controls. Benzene-associated neoplastic effects on the hematopoietic system were not observed in male or female rats. The incidences of mononuclear leukemia in dosed male rats were not different among dosed and vehicle control groups. In high dose female rats, the incidence of mononuclear cell leukemia (9/50) was somewhat greater than that in the vehicle controls (6/50); this increase was significant by the life table test (Appendix E, Table E2). These incidences are in the range of incidences observed in vehicle control female F344/N rats at the same laboratory (8/50-13/50) and therefore are not considered to be clearly related to administration of benzene. Further, the rates in concurrent vehicle controls are somewhat low compared with historic rates. Phenol, the primary metabolite of benzene, increased the incidence of mononuclear cell leukemia in male F344/N rats that received 2,500 ppm phenol in drinking water for 2 years, but this increase was not seen in male F344/N rats that received 5,000 ppm (vehicle control, 18/50, 36%; low dose, 30/50, 60%; $P<0.02$; high dose, 25/50, 50% [NCI, 1980; Huff, 1983]).

Zymbal Gland: Groups of modified sebaceous glands are located in the region of the external auditory canal in rats and mice and were originally described in 1933 by W. Zymbal and by C. Zawisch-Ossenitz apparently independently (Pliss, 1973). Some see a correspondence between the sebaceous Zymbal gland and the modified sebaceous ceruminous gland in humans (glands in the skin of the external auditory canal that secrete the watery component of the cerumen); others consider this relation as tenuous at best. Yet Pliss (1973) wrote that tumors of the auditory sebaceous glands in rats [and mice] are similar to tumors of the sebaceous glands in humans. Tumors of the auditory sebaceous (Zymbal) glands are uncommon (less than 1%) in F344/N rats and $B6C3F_1$ mice (Haseman et al., 1984). These neoplasms usually arise at the base of the ear, often invading the ear canal, and have both sebaceous and squamous differentiation. Pohl and Fouts (1983) found cytochrome P-450-dependent enzyme activity in homogenates of Zymbal glands from β-naphthoflavone-treated rats and mice. These authors suggested that chemical carcinogens can be metabolized to their initiating products in this gland.

The incidences of Zymbal gland carcinomas in mid and high dose male rats and in low, mid, and high dose female rats were greater than those in the vehicle controls (Table 30; see Tables 28 and 29) and exceeded the greatest incidences observed in corn oil vehicle historical controls (Appendix F, Table F21). The incidences of Zymbal gland carcinomas were significantly increased in mid and high dose male mice and in high dose female mice. In mid and high dose male mice and in high dose female mice, the incidences of epithelial hyperplasia of the Zymbal gland were also increased. The possible early occurrence and progression of these lesions was investigated by an examination of the Zymbal glands from the 10 animals per group killed after 12 months' exposure; no nonneoplastic or neoplastic pathologic effects were observed. One mid dose (50 mg/kg) female mouse had a small focus of acute inflammation.

Maltoni and Scarnato (1979) first reported Zymbal gland tumors in female (but not male) Sprague-Dawley rats exposed to benzene at 50 mg/kg (two tumors in 30 rats) and 250 mg/kg (5/32); control rats in this colony reportedly had a background incidence of 0.9% (Maltoni et al., 1983). In later inhalation experiments, Maltoni et al. (1982c, 1983, 1985) reported increases in Zymbal gland carcinomas; incidences in Sprague-Dawley rats appear to be: male--control, 0.6%; 200 ppm, 1.4%; 300 ppm, 5.3%;

TABLE 30. SUMMARY OF PRIMARY NEOPLASMS IN F344/N RATS AND B6C3F$_1$ MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

	Rats			Mice	
	Male	Female		Male	Female
Zymbal gland	+	+	Zymbal gland	+	+
Oral cavity	+	+	Lymphoma	+	+
Skin	+	–	Lung	+	+
			Harderian gland	+	±
			Mammary gland	–	+
			Preputial gland	+	NA
			Forestomach	±	±
			Ovary	NA	+
			Liver	–	±

+ = Increase relative to vehicle controls
± = Marginal increase relative to vehicle controls
– = No difference from vehicle controls
NA = Not applicable

female--control, 1.7%; 200 ppm, 1.7%; 300 ppm, 5.6%. Results from both inhalation and oral studies of Maltoni confirm the carcinogenic response of the Zymbal gland to benzene.

Skin: Benzene was associated with increased incidences of neoplasms of the oral cavity and skin of rats but not of mice (Table 30; see Tables 27 and 28). The incidences of squamous cell papillomas and squamous cell carcinomas of the skin in high dose male rats were greater than those in the vehicle controls and than those in the corn oil vehicle historical controls (Table F5).

These neoplasms of the skin and oral cavity in rats exposed to benzene are unusual in that adnexal and squamous elements are present. Even though these adenosquamous lesions contain sebaceous elements, they are distinct from the background sebaceous adenomas sometimes observed and appear to represent a benign form of an unusual benzene-related skin neoplasm. The skin neoplasms were considered to be a systemic effect of benzene metabolites, although the skin could have been topically exposed by the rats' grooming or by their exhaling unchanged benzene or its metabolites. Because benzene has been shown conclusively in numerous experiments not to induce skin tumors when applied topically, these skin lesions probably resulted from systemic exposure from reactive intermediates or from excretion of metabolites in saliva and then grooming. A less likely, yet possible, explanation for the oral lesions would be that intermediates are excreted by skin and thus the animals are exposed orally when they lick the skin. The increased incidences of uncommon squamous cell papillomas and squamous cell carcinomas of the oral cavity (including the palate, lip, and tongue) of dosed rats of each sex were probably due to a systemic effect of benzene-reactive intermediates. Squamous cell carcinomas of the oral cavity were also reported for Sprague-Dawley rats administered 500 mg/kg benzene by gavage for 104 weeks (Maltoni et al., 1983).

Lung: Administration of benzene was associated with increased incidences of alveolar epithelial hyperplasia in mid and high dose groups of male and female mice, increased incidences of alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male mice, alveolar/bronchiolar adenomas in high dose female mice, and alveolar/bronchiolar carcinomas in mid and high dose female mice (Table 30; see Tables 27 and 29). The increased incidences of alveolar/ bronchiolar neoplasms most likely result from a systemic effect of benzene rather than from a topical effect as a result of exhalation of unchanged benzene. Regardless of the route of exposure, benzene is apparently eliminated both in the expired air and in the urine (Rusch et al., 1977). For instance, 40% of a single oral dose of benzene was reported to be exhaled unchanged from the lungs

of rabbits (Parke and Williams, 1953); 70% of the benzene given subcutaneously to mice was found in expired air (Snyder, 1974).

Harderian Gland: First described by J. Harder in the 1600's, harderian glands are salt-secreting accessory lacrimal glands at the inner corner of the eye in vertebrates that have well-developed nictitating membranes; these excrete an unctuous fluid that facilitates the movement of the third eyelid. These glands are rudimentary in humans (Dorland, 1974). The harderian gland is racemose and horse-shoe shaped and lies deep within the orbit. The smaller arm lies superior to the larger arm, and these arms are connected by a narrow band. A single excretory duct opens at the base of the nictitating membrane (Tucker, 1979). The color of the gland varies from pink to dark grey. The gland is thought to produce and excrete porphyrin.

Focal hyperplasia of the harderian gland was observed at increased incidences in dosed mice of each sex (see Tables 27 and 29). The incidences of harderian gland adenomas and adenomas or carcinomas (combined) in dosed male and in high dose female mice were greater than those in the vehicle controls. The incidences in the mid and high dose female mice were greater than those previously observed in corn oil vehicle controls (10/50 and 10/47 vs 2/50; Table F18); the incidence in the concurrent controls (5/48) is also greater than that previously observed.

Harderian glands were examined from the 10 animals per group killed at 12 months. Mild localized epithelial hyperplasia was observed in 1/10 female vehicle controls, 1/10 low dose males, and 1/10 mid dose females; the mid dose female had a small adenoma near the hyperplastic focus. One of 10 low dose females had a small focus of necrosis and acute inflammation. One mid dose male had a small adenoma.

Preputial Gland: Administration of benzene to male mice was associated with significantly increased incidences of hyperplasia and squamous cell carcinomas of the preputial gland (see Tables 29 and 30). The incidences of squamous cell carcinomas in the mid dose (19/50) and high dose (31/49) groups greatly exceed the overall historical incidence (1/1,090). A possible explanation for this effect could be similar to that for the systemic mediated skin and oral cavity lesions seen in rats. However, the potential effects of benzene exposure by grooming cannot be fully discounted. No increases were observed for this lesion in male rats. Likewise, no increase in neoplasia was observed in the clitoral gland of female mice or rats (histogenetically related to the preputial gland).

Ovary: Increased incidences of various uncommon nonneoplastic and neoplastic lesions of the ovary (papillary cystadenoma, luteoma, granulosa cell tumors, tubular adenomas, benign mixed tumors, epithelial hyperplasia, and senile atrophy) were observed in benzene-exposed female mice (see Tables 27 and 29). The incidences of granulosa cell tumors in the high dose group and benign mixed tumors in mid and high dose female mice were increased compared with those in the vehicle controls. Benign mixed tumors and tubular adenomas of the ovary have not been reported previously in 1,028 corn oil vehicle female mice controls (Appendix F, Table F17), whereas the historical incidence of granulosa cell tumors or carcinomas is 3/1,028 as compared with 8/48 in the present study.

Mammary Gland: Incidences of carcinomas of the mammary gland in mid dose and high dose female mice and carcinosarcomas in high dose female mice were increased (see Tables 27 and 29). No comparable effects were seen in male mice or in male and female rats. Similarly, no increases in any nonneoplastic lesion were seen in any group.

Forestomach: Hyperkeratosis and acanthosis in the nonglandular stomach were observed at increased incidences in high dose male rats (see Table 27; Appendix C, Table C1). The incidences of hyperkeratosis in low dose male mice and mid and high dose female mice were greater than those in the vehicle controls. Although the incidences of squamous cell papillomas in high dose mice of each sex were not statistically greater than those in the vehicle controls, the incidences of these uncommon neoplasms in mice are noticably greater than those observed in corn oil vehicle historical controls. No "irritation" response and no neoplastic effects were observed in rats. Thus, the increased incidences of

squamous cell papillomas of the forestomach in mice may have been related to the administration of benzene.

Adrenal Gland: Focal hyperplasia of the zona fasciculata of the adrenal gland was observed at increased incidences in low dose rats of each sex (see Table 27). Hyperplasia of the adrenal capsule occurred at increased incidences in dosed mice of each sex. The incidence of pheochromocytomas in mid dose male mice was greater than that in the vehicle controls and in corn oil vehicle historical controls. In contrast, in dosed female mice, the incidence of pheochromocytomas was lower than that in the vehicle controls.

Liver: The incidences of heptocellular adenomas in low dose female mice and of hepatocellular adenomas or carcinomas (combined) in low and mid dose female mice were increased in comparison to those in the vehicle controls (see Tables 27 and 29). These incidences were greater than those previously observed in corn oil vehicle controls (Table F15). In male mice, the number of hepatocellular carcinomas in the mid dose group was marginally higher than that in the vehicle controls by the life table test (9/49 versus 17/50) but was not statistically increased by the appropriate adjusted analysis (incidental tumor test). Maltoni et al. (1983) reported that hepatocellular carcinomas were associated with inhalation exposure of Sprague-Dawley rats to benzene at 200-300 ppm for 4-7 hours per day for up to 104 weeks. In the current studies, the incidences of liver cell proliferative lesions were comparable among dosed and vehicle control groups of F344/N rats (Appendix C, Tables C1 and C2); a slight increase was observed for clear cell changes in mid dose male rats.

Most of the increased incidences of neoplasia were quite evident, and the statistical significance did not depend on which test procedure was used. However, for other lesions, the findings were considered marginal. For example, certain neoplasms generally regarded as nonlethal showed significant increases by life table analysis but not by the more appropriate incidental tumor test; these neoplasms included squamous cell papillomas of the forestomach in male and female mice. Nonetheless, these neoplasms are relatively uncommon in $B6C3F_1$ mice (<1%) and are probably associated with benzene administration; further, in both concurrent vehicle control groups, the incidences were somewhat high (male, 2/45; female, 1/42). In addition, some tumors showed apparent increases at lower doses which were not supported by similar high dose effects: hepatocellular adenomas or carcinomas in male and female mice and pheochromocytomas of the adrenal gland in male mice. Biologically, these must be considered as being possibly related to benzene exposure, given that the survival in the high dose groups was uniformly lower than that in vehicle controls, and hence perhaps these groups could have had reduced sensitivity for exhibiting a carcinogenic response. Also, pharmacokinetically, saturation of activation/deactivation systems do not allow consistent prediction as to which pathway will prevail. In any event, increased incidences of these tumors were considered not to be clearly due to benzene exposure.

The variety and multiplicity of toxic/carcinogenic responses to benzene exposure observed in these rodent studies raise the question of why the previous 10-15 experiments (6 dermal, 4 inhalation, 4 injection; IARC, 1982) failed to detect benzene-induced carcinogenicity. At least two possible explanations exist. Most of the earlier reported studies were less than adequate in comparison to current protocols and designs for showing no evidence of carcinogenicity; deficiencies included, for example, too few animals, no control animals, short-duration, low-level exposures, and so on. In addition, because it was known that benzene caused hematotoxicity in rodents and humans (including leukemia), a number of long-term studies by design did not include or report complete pathologic results; the possible implication is that major or singular emphasis was placed on the hematopoietic system, and lesser consideration was given to other organs or systems, thus accounting for the apparent lack of carcinogenic responses (or sensitivity) from rodents exposed to benzene.

More recent studies have been reported which collectively begin to accumulate evidence that benzene is indeed carcinogenic to laboratory animals and, in particular, to rats and mice (Maltoni and Scarnato, 1979; Snyder et al., 1980, 1984; Goldstein et al., 1982; Maltoni et al.,

1982a,b,c, 1983; Sellakumar et al., 1984). Individually, most of these studies provided marginal or speculative evidence. Maltoni et al. (1985) summarized convincing evidence from a series of experiments done in different species by both the oral and inhalation routes of exposure.

METABOLISM OR METABOLITES

Metabolism probably occurs most rapidly in the liver, where benzene is converted to benzene oxide (Figure 8; IARC, 1982), rearranges to form phenol, reacts with glutathione to form a premercapturic acid, or is hydrated to the dihydrodiol and then oxidized to catechol. Hydroquinone is also formed from phenol. Various benzoquinones are formed from the two dihydroxy metabolites. A lesser pathway proposed by Parke and Williams (1953) includes ring opening to muconaldehyde and muconic acid (Gibson et al., 1970; Rusch et al., 1977). Whether this takes place only in the gastrointestinal tract after oral administration remains unknown. Goldstein et al. (1982) offer the possibility of "ring expansion" to "benzene oxide-oxepin." Considering that benzene apparently lacks direct-acting mutagenicity or carcinogenicity, together with the apparent absence of (or weak) carcinogenic responses of the tested metabolites (see Introduction), one could speculate that "pre-phenol" benzene metabolic derivatives may possess or contribute to the observed toxic/carcinogenic properties. As early as 1949, Porteous and Williams (see Neuberger and Smith, 1983) argued that the toxic effects of benzene are related to its metabolites, and the authors separated these into toxic (free phenols) and nontoxic (conjugates) phases. Since then, a number of studies have been published by Williams and coworkers on benzene and other chemicals (Neuberger and Smith, 1983). In addition, the bone marrow has been shown to convert benzene to its known metabolites (Andrews et al., 1979; Irons et al., 1980). Irons et al. (1980) "clearly establish the capability of bone marrow to metabolize benzene independent of metabolism of the compound by the liver." The authors stress, however, that recovered metabolites represented considerably less than 1% of the benzene administered to male F344/N rats. Certain benzene intermediates or combinations thereof (see Figure 8) probably represent the toxic moiety or (composite) of benzene.

Nonetheless, evidence exists that metabolic production of reactive intermediates is required for expressing benzene-induced toxicity and probably carcinogenicity as well. As yet, the "active" chemical or chemicals have not been identified conclusively. Further metabolism studies in which the doses administered are the same as those used in these current studies should permit better determination of altered metabolism -- types and amounts of metabolites and pathways. The speculation that "pre-phenol" intermediates (or a cumulative metabolic effect) cause the observed benzene-associated toxicities remains to be proven.

GENETIC TOXICOLOGY

Rickert et al. (1979) showed that after rats were exposed to benzene, catechol and hydroquinone were retained in the bone marrow at higher concentrations and for longer times than phenol. Catechol and hydroquinone (or their metabolites) can be concentrated in bone marrow and lymphoid organs (Greenlee et al., 1981), and reports suggest that the toxicity of benzene may be related to the concentration of catechol and hydroquinone in bone marrow (Irons and Pfeifer, 1982).

The NTP (Appendix G) found that benzene administered by gavage induced micronuclei in male and female B6C3F$_1$ mice; males were more sensitive than females (Choy et al., 1985).

Although catechol and hydroquinone can induce sister-chromatid exchanges (SCE's) in human lymphocytes in vitro, benzene itself induces SCE's in vitro only after metabolic activation (Morimoto et al., 1983; Morimoto, 1983). In addition, Tice et al. (1982) and Erexson et al., (1985) have shown that benzene requires metabolic transformation in order to induce SCE's in bone marrow cells of mice in vitro.

Hydroquinone is not mutagenic in Salmonella (Epler et al., 1978; Florin et al., 1980; Gocke et

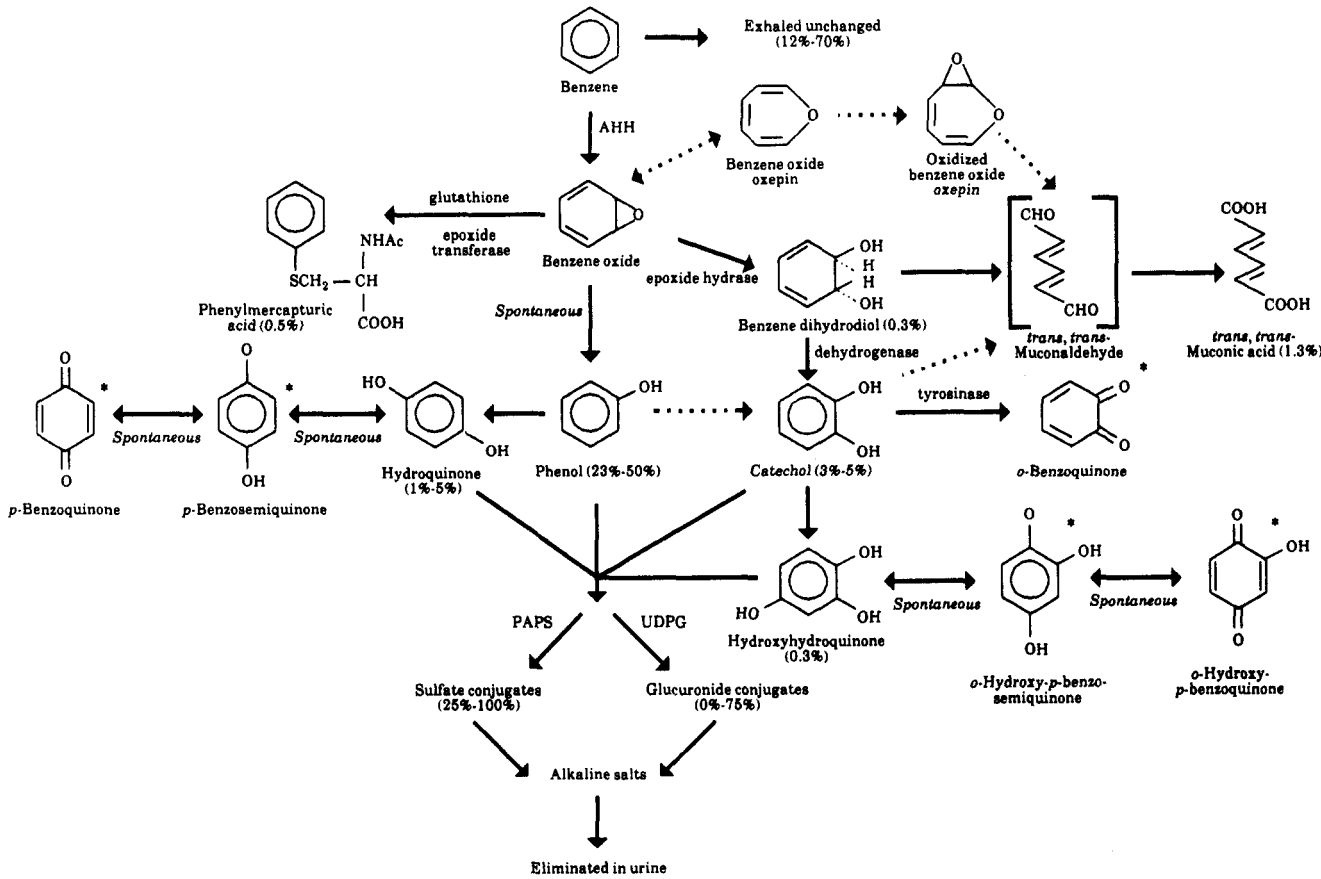


FIGURE 8. PATHWAYS OF BENZENE METABOLISM AND EXCRETION

Adapted from Parke and Williams, 1953; Laskin and Goldstein, 1977; Goldstein et al., 1982; Irons and Pfeifer, 1982; Pfeifer and Irons, 1983; Erexson et al., 1985; Sawahata et al., 1985. Values in parentheses are percentages of metabolic products detected in urine of animals (rabbits, rats, mice, dogs) or humans. Asterisks denote putative or demonstrated alkylating activity toward intracellular nucleophiles AHH = aryl hydrocarbon hydroxylase; UDPG = uridine diphosphate glucuronyl transferase; PAPS = 3'-phospho-adenosine-5'-phosphosulfate. Dashed lines indicate putative pathways. *trans, trans*-Muconaldehyde is a postulated intermediate.

al., 1981; Appendix G, Table G3). Hydroquinone induced SCE's in Chinese hamster ovary (CHO) cells (Table G4) and in cultured human lymphocytes (Morimoto and Wolff, 1980; Morimoto et al., 1983). In addition, hydroquinone also induces micronuclei in mice in vivo (Gocke et al., 1981; Tunek et al., 1982).

Catechol induced SCE's in cultured human lymphocytes (Morimoto and Wolff, 1980; Morimoto et al., 1983) and chromosomal aberrations in CHO cells (Stich et al., 1981). Tunek et al. (1982) found that catechol failed to induce micronuclei in mice in vivo. Wild et al. (1981) reported in an abstract that catechol did induce micronuclei in mice, but no data were presented.

Because these phenolic metabolites do not react with DNA or other biomacromolecules, because human lymphocytes have mixed-function oxidases (MFO's) and can metabolize many phenolic compounds (Selkirk et al., 1975; Nebert and Jensen, 1979), and because benzene can be metabolized to these phenolic derivatives in bone marrow in situ (Irons et al., 1980), Tunek et al. (1980) and Morimoto et al. (1983) have suggested that compounds formed by further metabolism of catechol and hydroquinone might be responsible for the biologic effects of benzene. These authors did not mention benzene oxide or other potential metabolites formed before the phenolic stage.

Morimoto et al. (1983) observed that rat liver S9 enhanced the ability of catechol and hydroquinone to induce SCE's in cultured human lymphocytes. Tunek et al. (1978, 1980) have shown that hydroquinone is further converted to *p*-benzosemiquinone and *p*-benzoquinone. These metabolites of hydroquinone, in addition to the metabolites of catechol (presumably *o*-benzoquinone and *o*-hydroxy-*p*-benzosemiquinone), may contribute to the genetic toxicity induced by benzene.

Numerous studies have documented a variety of chromosomal aberrations in humans who have benzene-associated myelotoxicity. Almost all humans with benzene-associated leukemia were exposed to other chemicals, although exposure to benzene was common to all. The possibility exists, albeit equivocally, that other chemicals in addition to benzene may have been involved in the development of the leukemia, and this possibility could help explain the failure to reproduce benzene-associated leukemia in the present NTP studies or in other such studies in experimental animals (Dean, 1978); nonetheless, benzene caused lymphomas in both sexes of mice (see Table 29) in these studies. Cronkite et al. (1984, 1985) report an increase in lymphomas in female C57BL/6 mice exposed at 300 ppm for 16 weeks and observed until death. These authors suggest that prolonged exposures may suppress the incidence in lymphomas or shorten the life span of mice, so lymphomas cannot be observed. Even so, perhaps rodents may not be adequate models for human leukemogenesis. The malignant cells of most neoplasias, including lymphomas and leukemias, have chromosomal abnormalities, and for most, specific chromosomal defects are associated with specific neoplasias (Yunis, 1983). As yet, the advanced chromosome banding techniques have not been applied to benzene-exposed humans. Thus, the association of specific chromosomal abnormalities with various benzene-associated neoplasias awaits further study.

Another unexplained disparity is the observation that benzene (or metabolites) causes cytogenetic abnormalities, such as chromosomal aberrations, SCE's, and micronuclei, but does not cause gene mutations. All of the positive results obtained with benzene have been obtained from in vivo systems, and all of these systems measure a cytogenetic endpoint. The reason is that there are no in vivo, somatic-cell, gene-mutation assays that have been used with an extensive number and variety of classes of chemicals. Such assays are being developed, and it will be interesting to see if benzene is positive in such an assay. If it is not, then benzene will have the distinction of being one of the few chemicals known which is solely a clastogen (an agent that breaks chromosomes) but does not cause mutations. If benzene is capable of inducing gene mutation in vivo, then the disparity between the positive in vivo cytogenetic results and the negative in vitro gene mutation results would be explained by the fact that reactive metabolites of benzene are formed in vivo. Therefore, an in vivo assay is required to detect gene mutations that are induced by these metabolites. Further

work should resolve this disparity. These and other genetic toxicology studies on benzene have been summarized by Dean (1985).

INITIATED EXPERIMENTS

To further investigate the role of metabolism in the toxicology and carcinogenesis of benzene, NTP has initiated studies that involve both oral and inhalation exposure to benzene in F344/N rats and in $B6C3F_1$ mice. Animals will be exposed for 5 days to radioactively labeled benzene over a wide dose range, the highest dose to exceed that used in these carcinogenicity studies. Tissue distribution and excretion will be compared and benzene metabolites (including phenol, catechol, hydroquinone, and muconic acid) quantitated in identified target organs and excreta. Binding of benzene metabolites to DNA and other macromolecules will be investigated. In addition, the effect of dose rate in inhalation exposures on metabolism and distribution will be examined. These studies should help answer the question of whether dose-response relationships are linear at levels similar to those involved in occupational exposure. Equally, results from these experiments will aid in determining whether species and/or strain differences in pharmacokinetic parameters correlate with those observed in benzene carcinogenesis. Cytogenetic effects of benzene exposure over the wide dose range will also be investigated. Morphologic and genetic endpoints will be correlated with the levels of benzene and metabolites present in the peripheral blood cells and in bone marrow.

In summary, benzene has been long recognized as a hazardous chemical in the workplace and to a lesser extent in the general environment. A positive association has been established between occupational exposure to benzene and aplastic anemia and acute myelogenous leukemia in workers. Definitive evidence now exists that benzene induces neoplasia in laboratory rodents (see Table 30). Whether one or several metabolites (alone or in combination with benzene) induce the toxic, mutagenic, and carcinogenic effects awaits further study.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** of benzene for male F344/N rats, for female F344/N rats, for male $B6C3F_1$ mice, and for female $B6C3F_1$ mice. For male rats, benzene caused increased incidences of Zymbal gland carcinomas, squamous cell papillomas and squamous cell carcinomas of the oral cavity, and squamous cell papillomas and squamous cell carcinomas of the skin. For female rats, benzene caused increased incidences of Zymbal gland carcinomas and squamous cell papillomas and squamous cell carcinomas of the oral cavity. For male mice, benzene caused increased incidences of Zymbal gland squamous cell carcinomas, malignant lymphomas, alveolar/bronchiolar carcinomas and alveolar/bronchiolar adenomas or carcinomas (combined), harderian gland adenomas, and squamous cell carcinomas of the preputial gland. For female mice, benzene caused increased incidences of malignant lymphomas, ovarian granulosa cell tumors, ovarian benign mixed tumors, carcinomas and carcinosarcomas of the mammary gland, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and Zymbal gland squamous cell carcinomas.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

1. Aksoy, M. (1985) Malignancies due to occupational exposure to benzene. Am. J. Ind. Med. 7:395-402.

2. American Journal of Industrial Medicine (1985) 7:365-498.

3. American Petroleum Institute (API) (1982) Inhalation Teratology Study in Rats: Benzene. API Med. Res. Publ. No. 30-30224.

4. Ames, B.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

5. Anderson, D.; Richardson, C. (1981) Issues relevant to the assessment of chemically induced chromosome damage *in vivo* and their relationship to chemical mutagenesis. Mutat. Res. 90:261-272.

6. Andrews, L.; Sasame, H.; Gillette, J. (1979) ^{3}H-Benzene metabolism in rabbit bone marrow. Life Sci. 25:567-572.

7. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

8. Bartsch, H.; Malaveille, C.; Camus, A.; Martel-Planche, G.; Brun, G.; Hautefeuelle, A.; Sabadie, N.; Barbin, A.; Kuroki, T.; Drevon, C.; Piccoli, C.; Montesano, R. (1980) Validation and comparative studies of 180 chemicals with *S. typhimurium* strains and V79 chinese hamster cells in the presence of various metabolizing systems. Mutat. Res. 76:1-50.

9. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

10. Blank, I.; McAuliffe, D. (1985) Penetration of benzene through human skin. J. Invest. Derm. 85:522-526.

11. Bolcsak, L.; Nerland, D. (1983) Inhibition of erythropoiesis by benzene and benzene metabolites. Toxicol. Appl. Pharmacol. 69:363-368.

12. Boorman, G.; Eustis, S. (1984) Proliferative lesions of the exocrine pancreas in male F344/N rats. Environ. Health Perspect. 56:213-217.

13. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S.; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

14. Boutwell, R.; Bosch, D. (1959) The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19:413-424.

15. Boyland, E.; Busby, E.; Dukes, C.; Grover, P.; Manson, D. (1964) Further experiments on implantation of materials into the urinary bladder of mice. Br. J. Cancer 18:575-581.

16. Brief, R.; Lynch, J.; Bernath, T.; Scala, R. (1980) Benzene in the workplace. Am. Ind. Hyg. Assoc. J. 41:616-623.

17. Carlson; Brewer (1953) Toxicity studies on hydroquinone. Proc. Soc. Exp. Biol. 84:684-688.

18. Chang, S.; Peterson, R. (1977) Symposium: The basis of quality in muscle foods. Recent developments in the flavor of meat. J. Food Sci. 42:298-305.

19. Chemical & Engineering News (1980) Key chemicals. Benzene. November 17, p. 20.

20. Chemical & Engineering News (1985) Top 50 Chemical Products. May 6, pp. 11-20.

21. Choy, W.; MacGregor, J.; Shelby, M.; Maronpot, R. (1985) Induction of micronuclei by benzene in B6C3F$_1$ mice: Retrospective analysis of peripheral blood smears from the NTP carcinogenesis bioassay. Mutat. Res. 143:55-59.

22. Cornish, H.; Ryan, R. (1965) Metabolism of benzene in nonfasted, fasted, and aryl-hydroxylase inhibited rats. Toxicol. Appl. Pharmacol. 7:767-771.

23. Cotruvo, J.; Simmon, V.; Spanggord, R. (1977) Investigation of mutagenic effects of products of ozonation reactions in water. Ann. N.Y. Acad. Sci. 298:124-140.

24. Cox, D. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

25. Criteria Group for Occupational Standards (CGOS) (1982) Scientific basis for Swedish occupational standards. Arbete och Halsa 9:24-37.

26. Cronkite, E.; Bullis, J.; Inoue, T.; Drew, R. (1984) Benzene inhalation produces leukemia in mice. Toxicol. Appl. Pharmacol. 75:358-361.

27. Cronkite, E.; Drew, R.; Inoue, T.; Bullis, J. (1985) Benzene hematotoxicity and leukemogenesis. Am. J. Ind. Med. 7:447-456.

28. Davis, D. (1986) Reproductive risks of benzene: Need for additional study. Submitted for publication.

29. Dean, B. (1969) Chemical-induced chromosome damage. Lab. Anim. 3:157-174.

30. Dean, B. (1978) Genetic toxicology of benzene, toluene, xylenes and phenols. Mutat. Res. 47:75-97.

31. Dean, B. (1985) Recent findings on the genetic toxicology of benzene, toluene, xylenes and phenols. Mutat. Res. 154:153-181.

32. DeCoufle, P.; Blattner, W.; Blair, A. (1983) Mortality among chemical workers exposed to benzene and other agents. Environ. Res. 30:16-25.

33. Deichmann, W.; MacDonald, W.; Bernal, E. (1963) The hemopoietic tissue toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5:201-224.

34. Delore, P.; Borgomano, C. (1928) Acute leukaemia following benzene poisoning. On the toxic origin of certain acute leukaemias and their relation to serious anaemias. (Fr.) J. Med. Lyon 9:227-233.

35. Deutsche Forschungsgemeinschaft (1974) Benzol am arbeitsplatz (Benzene in the workplace). Weinheim, Verlag Chemie Gmbh.

36. Diaz, M.; Reiser, A.; Braier, L.; Diez, J. (1980) Studies on benzene mutagenesis. I. The micronucleus test. Experientia 36:297-299.

37. Dixon, W.; Massey, F. (1951) Introduction to Statistical Analysis. New York: McGraw Hill, pp. 145-147.

38. Dorland Illustrated Medical Dictionary (1974) 25th ed. Philadelphia, PA: W.B. Saunders Co.

39. Dowty B.; Carlisle, D.; Laseter, J. (1975) New Orleans drinking water sources tested by gas chromatography-mass spectrometry. Occurrence and origin of aromatics and halogenated aliphatic hydrocarbons. Environ. Sci. Technol. 9:762-765.

40. Dunnett, C. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50:1096-1121.

41. Dunnett, C. (1964) New tables for multiple comparisons with a control. Biometrics 20:482-491.

42. Egilsson, V.; Evans, I.; Wilkie, D. (1979) Toxic and mutagenic effects of carcinogens on the mitochondria of *Saccaromyces cerevisiae*. Mol. Gen. Genet. 174:39-46.

43. Epler, J.; Larimer, F.; Rao, T.; Nix, C.; Ho, T. (1978) Energy-related pollutants in the environment: Use of short-term tests for mutagenicity in the isolation and identification of biohazards. Environ. Health Perspect. 27:11-20.

44 . Erexson, G.; Wilmer, J.; Kligerman, A. (1985) Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites *in vitro*. Cancer Res. 45:2471-2477.

45. Federal Register (Fed. Reg.) (1985) 50(237):50512-50586.

V. REFERENCES

46. Florin, I.; Rutberg, L.; Curvall, M.; Enzell, C. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15:219-232.

47. Flury, F. (1928) II. Modern occupational intoxications. II(a). Modern occupational intoxications from the aspect of pharmacology and toxicology. Arch. Exp. Pathol. Pharmakol. 138:65-82.

48. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

49. Gerarde, H. (1956) Toxicological studies on hydrocarbons. AMA Arch. Ind. Health. 13:468-474.

50. Gerner-Smidt, P.; Friedrich, U. (1978) The mutagenic effect of benzene, toluene, and xylene studied by the SCE technique. Mutat. Res. 58:313-316.

51. Gibson, D.; Cardini, G.; Maseles, F.; Kallio, R. (1970) Oxidative degradation of aromatic hydrocarbons by microorganisms. IV. Incorporation of oxygen-18 into benzene by *Pseudomonas putida*. Biochemistry 9:1631-1635.

52. Gocke, E.; King, M.-T.; Eckardt, K.; Wild, D. (1981) Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat. Res. 90:91-109.

53. Goldstein, B. (1977) Hematotoxicity in humans. J. Toxicol. Environ. Health 2:69-105.

54. Goldstein, B. (1983) Benzene Toxicity: Review of Recent Literature. Report prepared for the American Petroleum Institute, February 3.

55. Goldstein, B. (1985) Risk assessment and risk management of benzene by the Environmental Protection Agency. Hoel, D.; Merrill, R.; Perera, F., Eds.: Risk Quantitation and Regulatory Policy. Cold Spring Harbor Laboratory.

56. Goldstein, B.; Snyder, C.; Laskin, A.; Bromberg, I.; Albert, R. (1982) Myelogenous leukemia in rodents inhaling benzene. Toxicol. Lett. 13(3-4):169-173.

57. Goto, K.; Maeda, S.; Kano, Y.; Sugimura, T. (1978) Factors involved in differential Giemsa-staining of sister chromatids. Chromosoma 66:351-359.

58. Green, J.; Leong, B.; Laskin, S. (1978) Inhaled benzene fetotoxicity in rats. Toxicol. Appl. Pharmacol. 46:9-18.

59. Green, J.; Snyder, C.; LoBue, J.; Goldstein, B.; Albert, R. (1981) Acute and chronic dose/response effect of benzene inhalation on the peripheral blood, bone marrow, and spleen cells of CD-1 male mice. Toxicol. Appl. Pharmacol. 59:204-214.

60. Greenlee, W.; Gross, E.; Irons, R. (1981) Relationship between benzene toxicity and disposition of ^{14}C-labelled benzene metabolites in the rat. Chem.-Biol. Interact. 33:285-299.

61. Grossenbacher, J.; Lob, M. (1982) Occupational exposure to benzene: Follow-up study (Abst). Schweiz. Med. Wochenschr. 112:1858.

62. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

63. Haseman, J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

64. Haseman, J.; Huff, J.; Rao, G.; Arnold, J.; Boorman, G.; McConnell, E. (1985) Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. J. Natl. Cancer Inst. 75:975-984.

65. Hecht, S.; Thorne, R.; Maronpot, R.; Hoffmann, D. (1975) A study of tobacco carcinogenesis. XIII. Tumor-promoting subfractions of the weakly acidic fraction. J. Natl. Cancer Inst. 55:1329-1336.

66. Hecht, S.; Carmella, S.; Mori, H.; Hoffmann, D. (1981) A study of tobacco carcinogenesis. XX. Role of catechol as a major cocarcinogen in the weakly acidic fraction of smoke condensate. J. Natl. Cancer Inst. 66:163-169.

67. Hermann, M. (1981) Synergistic effects of individual polycyclic aromatic hydrocarbons on the mutagenicity of their mixture. Mutat. Res. 90:399-409.

68. Hite, M.; Pecharo, M.; Smith, I.; Thorton, S. (1980) Effect of benzene in the micronucleus test. Mutat. Res. 77:149-155.

69. Ho, C.; Clark, B.; Guerin, M.; Barkenbus, B.; Rao, T.; Epler, J. (1981) Analytical and biological analyses of test materials from the synthetic fuels technologies. IV. Studies of chemical structure mutagenic activity relationships of aromatic nitrogen compounds relevant to synfuels. Mutat. Res. 85:335-345.

70. Holmberg, B.; Lundberg, P. (1985) Benzene: Standards, occurrence, and exposure. Am. J. Ind. Med. 7:375-383.

71. Hudak, A.; Ungvary, G. (1978) Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology 11:55-63.

72. Huff, J. (1983) Carcinogenesis results on seven amines, two phenols, and one diisocyanate used in plastics and synthetic elastomers. Jarvisalo, J.; Pfaffli, P.; Vainio, H., Eds.: Industrial Hazards of Plastics and Synthetic Elastomers. New York: Alan R. Liss, Inc., pp. 347-363.

73. Hunter, D. (1978) The Diseases of Occupations, 6th ed. London: Hodder & Stoughton, pp. 489-499.

74. Infante, P. (1978) Leukemia among workers exposed to benzene. Tex. Rep. Biol. Med. 37:153-161.

75. Infante, P.; White, M. (1983) Benzene: Epidemiologic observations of leukemia by cell type and adverse health effects associated with low-level exposure. Environ. Health Persp. 52:75-82.

76. Infante, P.; White, M. (1985) Projections of leukemia risk associated with occupational exposure to benzene. Am. J. Ind. Med. 7:403-413.

77. Infante, P.; Rinsky, R.; Wagoner, J.; Young, R. (1977) Leukemia in benzene workers. Lancet July 9, pp. 76-78.

78. International Agency for Research on Cancer (IARC) (1977) *para*-Quinone. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals, Vol. 15. Lyon, France: IARC, pp. 255-264.

79. International Agency for Research on Cancer (IARC) (1982) Benzene. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Some Industrial Chemicals and Dyestuffs, Vol. 29. Lyon, France: IARC, pp. 95-148.

80. Irons, R.; Pfeifer, R. (1982) Benzene metabolites: Evidence for an epigenetic mechanism of toxicity. Environ. Sci. Res. 25:241-256.

81. Irons, R.; Heck, H.; Moore, B.; Muirhead, K. (1979) Effects of short-term benzene administration on bone marrow cell cycle kinetics in the rat. Toxicol. Appl. Pharmacol. 51:399-409.

82. Irons, R.; Dent, J.; Baker, T.; Rickert, D. (1980) Benzene is metabolized and covalently bound in bone marrow in situ. Chem.-Biol. Interact. 30:241-245.

83. Kaden, D.; Hites, R.; Thilly, W. (1979) Mutagenicity of soot and associated polycyclic aromatic hydrocarbons to *Salmonella typhimurium*. Cancer Res. 39:4152-4159.

84. Kale, P.; Baum, J. (1983) Genetic effects of benzene in *Drosophila melanogaster* males. Environ. Mutagen. 5:223-226.

85. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

86. Kastenbaum, N.; Bowman, K. (1970) Tables for determining the statistical significance of mutation frequencies. Mutat. Res. 9:527-549.

V. REFERENCES

87. Kimura, E.; Ebert, D.; Dodge, P. (1971) Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

88. Kishizawa, F. (1954) Carcinogenic action of *para*-benzoquinone on the lung of mice by the experimental inhalation (Report 1). Gann 45:389-391.

89. Kishizawa, F. (1955) Carcinogenic action of benzoquinone on the lung of mice by the experimental inhalation (Report 2). Gann 46:359-361.

90. Kishizawa, F. (1956) Carcinogenic action of *para*-benzoquinone on the lung of mice by the experimental inhalation (Report 3). Gann 47:601-603.

91. Kissling, M.; Speck, B. (1971) Chromosome aberrations in experimental benzene intoxication. Helv. Med. Acta. 36:59-66.

92. Koizumi, A.; Dobashi, Y.; Tachibana, Y.; Tsuda, K.; Katsunuma, H. (1974) Cytokinetic and cytogenetic changes in cultured human leukocytes and Hela cells induced by benzene. Ind. Health 12:23-29.

93. Kuna, R.; Kapp, R. (1981) The embryotoxic/teratogenic potential of benzene vapor in rats. Toxicol. Appl. Pharmacol. 57:1-7.

94. Laskin, S.; Goldstein, B., Eds. (1977) Benzene toxicity: A critical evaluation. J. Toxicol. Environ. Health Suppl. November 2.

95. Lauwerys, R. (1979) Industrial Health and Safety. *Human Biological Monitoring of Industrial Chemicals. 1. Benzene.* Luxembourg, Commission of the European Communities.

96. Lebowitz, H.; Brusick, D.; Matheson, D.; Jagannath, D.; Reed, M.; Goode, S.; Roy, G. (1979) Commonly used fuels and solvents evaluated in a battery of short-term bioassays. Environ. Mutagen. 1:172-173.

97. Lehman, A.; Fitzhugh, O.; Nelson, A.; Woodard, G. (1951) The pharmacological evaluation of antioxidants. Adv. Food Res. 3:197-208.

98. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

99. Lyon, J. (1975) Mutagenicity studies with benzene (Abstract). Diss. Abstr. Int. B. 36:5537.

100. MacGregor, J.; Schlegel, R.; Choy, W.; Weir, C. (1983) Micronuclei in circulating erythrocytes: A rapid screen for chromosomal damage during routine toxicity testing in mice. Hayes, A.; Schnell, R.; Miya, T., Eds.: Developments in the Science and Practice of Toxicology. New York, Elsevier, pp. 555-558.

101. Maltoni, C.; Scarnato, C. (1979) First experimental demonstration of the carcinogenic effects of benzene: Long-term bioassays on Sprague-Dawley rats by oral administration. Med. Lav. 70:352-357.

102. Maltoni, C.; Conti, B.; Scarnato, C. (1982a) Squamous cell carcinomas of the oral cavity in Sprague-Dawley rats following exposure to benzene by ingestion. First experimental demonstration. Med. Lav. 73(4):441-445.

103. Maltoni, C.; Cotti, G.; Valgimigli, L.; Mandrioli, A. (1982b) Hepatocarcinomas in Sprague-Dawley rats following exposure to benzene by inhalation. First experimental demonstration. Med. Lav. 73(4):446-450.

104. Maltoni, C.; Cotti, G.; Valgimigli L.; Mandriole, A. (1982c) Zymbal gland carcinomas in rats following exposure to benzene by inhalation. Am. J. Ind. Med. 3:11-16.

105. Maltoni, C.; Conti, B.; Cotti, G. (1983) Benzene: A multipotential carcinogen. The up-to-date results of the long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4:589-630.

106. Maltoni, C.; Conti, B.; Cotti, G.; Belpoggi, F. (1985) Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: Current results and ongoing research. Am. J. Ind. Med. 7:415-446.

107. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

108. Maronpot, R.; Boorman, G. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

109. McCarroll, N.; Keech, B.; Piper, C. (1981a) A microsuspension adaptation of the Bacillus subtilis "rec" assay. Environ. Mutagen. 3:607-616.

110. McCarroll, N.; Piper, C.; Keech, B. (1981b) An E coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ. Mutagen. 3:429-444.

111. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. (in press).

112. Mehlman, M., Ed. (1985) Benzene: Scientific Update. Proceedings of the International Conference on Benzene Sponsored by the Collegium Ramazzini, New York, NY, November 3-4, 1983. New York: Alan R. Liss, Inc. 132 p.

113. Mehlman, M.; Schreiner, C.; Mackerer, C. (1981) Current status of benzene teratology: A brief review. J. Environ. Pathol. Toxicol. 4:123-131.

114. Merck Index (1976) 9th ed. Rahway, NJ: Merck and Company, Inc., p. 138.

115. Meyne, J.; Legator, M. (1980) Sex-related differences in cytogenetic effects of benzene in the bone marrow of swiss mice. Environ. Mutagen. 2:43-50.

116. Miller, R. (1981) Simultaneous Statistical Inference, 2nd ed. New York: Springer-Verlag, Inc.

117. Morimoto, K. (1974) Combined cytogenetic effects of benzene and radiation on cultured human lymphocytes. Jpn. J. Ind. Health 17:106-107.

118. Morimoto, K. (1983) Induction of sister chromatid exchanges and cell division delays in human lymphocytes by microsomal activation of benzene. Cancer Res. 43:1130-1334.

119. Morimoto, K.; Wolff, S. (1980) Increase of sister chromatid exchanges and perturbations of cell division kinetics in human lymphocytes by benzene metabolites. Cancer Res. 40:1189-1193.

120. Morimoto, K.; Wolff, S.; Koizumi, A. (1983) Induction of sister-chromatid exchanges in human lymphocytes by microsomal activation of benzene metabolites. Mutat. Res. 119:355-360.

121. National Cancer Institute (NCI) (1980) Bioassay of Phenol for Possible Carcinogenicity, TR No. 203. Washington, D.C.: National Institutes of Health, Department of Health and Human Services.

122. National Institute for Occupational Safety and Health (NIOSH) (1977) Occupational Diseases. A Guide to Their Recognition. Washington, D.C.: U.S. Department of Health, Education, and Welfare, pp. 235-238.

123. National Research Council (NRC) (1980) Drinking Water and Health, Vol. 3. Washington, D.C.: National Academy of Sciences, pp. 80-86, 261-262.

124. Nebert, D.; Jensen, N. (1979) The *Ah* locus: genetic regulation of the metabolism of carcinogens, drugs, and other environmental chemicals by cytochrome P-450-mediated monooxygenases. Crit. Rev. Biochem. 6:401-437.

125. Neuberger, A.; Smith, R (1983) Richard Tecwyn Williams: The man, his work, his impact. Drug Metab. Rev. 14:559-607.

126. Nylander, P-O.; Olofsson, H.; Rasmuson, B.; Svahlin, H. (1978) Mutagenic effects of petrol in *Drosophila melanogaster* I. Effects of benzene and 1,2-dichloroethane. Mutat. Res. 57:163-167.

127. Ott, M.; Townsend, J.; Fishbeck, W.; Langer, R. (1978) Mortality among individuals occupationally exposed to benzene. Arch. Environ. Health 33:3-10.

V. REFERENCES

128. Parke, D.; Williams, R. (1953) The metabolism of benzene containing [$^{14}C_1$]benzene. Biochem. J. 54:231-238.

129. Perry, P.; Wolff, S. (1974) New Giemsa method for the differential staining of sister chromatids. Nature (London) 251:156-158.

130. Pfeifer, R.; Irons, R. (1983) Quinones and sulfhydryl-dependent immunotoxicity. Proceedings of the 13th Conference on Environmental Toxicology (Nov. 16-18, 1982). AFAMRL TR-82-101. U.S. Air Force Aerospace Medical Research Laboratory, Dayton, OH, pp. 106-135.

131. Pliss, G. (1973) Tumours of the auditory sebaceous glands. Turusov, V., Ed.: Pathology of Tumours in Laboratory Animals, Vol. I. Tumours of the Rat, Part 1. Lyon, France: International Agency for Research on Cancer, pp. 23-30.

132. Pohl, R.; Fouts, J. (1983) Cytochrome P-450-dependent xenobiotic metabolizing activity in Zymbal's gland, a specialized sebaceous gland of rodents. Cancer Res. 43:3660-3662.

133. Purcell, W. (1978) Benzene. Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 3, 3rd ed. New York: John Wiley & Sons, Inc., pp. 744-771.

134. Rickert, D.; Baker, T.; Bus, J.; Barrow, C.; Irons, R. (1979) Benzene disposition in the rat after exposure by inhalation. Toxicol. Appl. Pharmacol. 49:417-423.

135. Rinsky, R.; Smith, A.; Hornung, R.; Filloon, T.; Young, R.; Okun, A.; Landrigan, P. (1986) Benzene and Leukemia: An Epidemiologic Risk Assessment. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health. 24 p. Submitted for publication.

136. Roe, F.; Salaman, M. (1955) Further studies on incomplete carcinogenesis: Triethylene melamine (T.E.M.), 1,2-benzanthracene and β-propiolactone as initiators of skin tumour formation in the mouse. Br. J. Cancer 9:177-203.

137. Rosenkranz, H.; Leifer, Z. (1980) Determining the DNA-modifying activity of chemicals using DNA-polymerase-deficient *Escherichia coli*. de Serres, F.; Hollaender, A., Eds.: Chemical Mutagens: Principles and Methods for Their Detection, Vol. 6. New York: Plenum Publishers, pp. 109-147.

138. Rusch, G.; Leong, B.; Laskin, S. (1977) Benzene metabolism. J. Toxicol. Environ. Health Supplement 2, p. 23-36.

139. Sabourin, P.; Chen, B.; Henderson, R.; Lucier, G.; Birnbaum, L. (1986) Effect of dose on absorption and excretion of ^{14}C benzene administered orally or by inhalation (Abst.) The Toxicologist 6:163.

140. Sadtler Research Laboratories: Sadtler Standard Spectra. Philadelphia: Sadtler Research Laboratories, IR 579, UV No. 1961, NMR No. 3429M.

141. Salaman, M.; Glendenning, O. (1957) Tumour promotion in mouse skin by sclerosing agents. Br. J. Cancer 11:434-444.

142. Santesson, C. (1897) Chronic poisoning with coal tar benzene; four deaths. Clinical and pathological-anatomical observations of several colleges and illustrating animal experiments (Ger.) Arch. Hyg. (Munchen) 31:336-376.

143. Sarto, F; Cominato, I.; Pinton, A.; Brovedani, P.; Merier, E.; Peruzzi, M.; Bianchi, V.; Levis, A. (1984) A cytogenetic study on workers exposed to low concentrations of benzene. Cytogenetics 5:827-832.

144. Sawahata, T.; Rickert, D.; Greenlee, W. (1985) Metabolism of benzene and its metabolites in bone marrow. Irons, R., Ed.: Toxicology of the Blood and Bone Marrow. New York: Raven Press, pp. 141-148.

145. Schairer, L.; Sautkulis, R. (1982) Detection of ambient levels of mutagenic atmospheric pollutants with the higher plant Tradescantia. Klekowski, E., Ed.: Environment Mutagenesis, Carcinogenesis and Plant Biology, Vol. II. Praeger, pp. 154-194.

146. Schairer, L.; Van't Hof, J.; Haynes, C.; Burton, R.; de Serres, F. (1978) Measurement of biological activity of ambient air mixtures using a mobile laboratory for *in situ* exposures: Preliminary results from the *Tradescantia* plant test system. Waters, M.; et al., Eds.: Application of Short-term Bioassays in the Fractionation and Analysis of Complex Environmental Mixtures. EPA/600/9-78-027.

147. Schwetz, B. (1983) A review of the developmental toxicity of benzene. Advances in Modern Environmental Toxicology. Princeton Scientific Publishers, Princeton, NJ, pp. 17-21.

148. Selkirk, J.; Croy, R.; Whitlock, Jr., J.; Gelboin, H. (1975) In vitro metabolism of benzo(a)pyrene by human-liver microsomes and lymphocytes. Cancer Res. 35:3651-3655.

149. Sellakumar, A.; Albert, R.; Snyder, C. (1984) Carcinogenicity of benzene. Proc. Am. Assoc. Cancer Res. 25:75 (Abstr.).

150. Selling, L. (1916) Benzol as a leucotoxin. Studies on the degeneration and regeneration of the blood and hematopoietic organs. Johns Hopkins Hosp. Rep. 17:83-142.

151. Shahin, M.; Fournier, F. (1978) Suppression of mutation induction and failure to detect mutagenic activity with Athabasca tar sand fractions. Mutat. Res. 58:29-34.

152. Simmon, V.; Kauhanen, K.; Tardiff, R. (1977) Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2:249-258.

153. Siou, G.; Conan, L.; el Haitem, M. (1981) Evaluation of the clastogenic action of benzene by oral administration with 2 cytogenetic techniques in mouse and Chinese hamster. Mutat. Res. 90:273-278.

154. Snyder, C.; Goldstein, B.; Sellakumar, A.; Bromberg, I.; Laskin, S; Albert, R. (1980) The inhalation toxicology of benzene: Incidence of hematopoietic neoplasms and hematotoxicity in AKR/J and C57BL/6J mice. Toxicol. Appl. Pharmacol. 54:323-331.

155. Snyder, C.; Goldstein, B.; Sellakumar, A.; Albert, R. (1984) Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene. Am. J. Ind. Med. 5:429-434.

156. Snyder, R. (1974) Relation of benzene metabolism to benzene toxicity. Braun, D., Ed.: Symposium on Toxicology of Benzene and Alkylbenzenes. Pittsburgh, PA: Industrial Health Foundation, p. 44.

157. Snyder, R.; Kocsis, J. (1975) Current concepts of chronic benzene toxicity. Crit. Rev. Toxicol. 3:265-288.

158. Stich, H.; Rosin, M.; Wu, C.; Powrie, W. (1981) The action of transition metals on the genotoxicity of simple phenols, phenolic acids and cinnamic acids. Cancer Lett. 14:251-260.

159. Susten, A.; Dames, B.; Burg, J.; Niemeier, R. (1985) Percutaneous penetration of benzene in hairless mice: An estimate of dermal absorption during tire-building operations. Am. J. Ind. Med. 7:323-335.

160. Svirbely, J.; Dunn, R.; von Oettingen, W. (1943) The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J. Ind. Hyg. Toxicol. 25:366-373.

161. Takizawa, N. (1940) Über die experimentelle Erzeugung der Haut- und Lungenkrebse bei der Maus durch Bepinselung mit Chinone. Gann 34:158-160.

162. Tanooka, H. (1977) Development and application of *Bacillus subtilis* test systems for mutagens, involving DNA-repair deficiency and suppressible auxotrophic mutations. Mutat. Res. 42:19-32.

163. Tarone, R. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

164. Tice, R.; Costa, D.; Drew, R. (1980) Cytogenetic effects of inhaled benzene in murine bone marrow: Induction of sister chromatid exchanges, chromosomal aberrations, and cellular proliferation inhibition in DBA/2 mice. Proc. Natl. Acad. Sci. USA 77:2148-2152.

165. Tice, R.; Fogt, T.; Costa, D. (1982) Cytogenetic effects of inhaled benzene in murine bone marrow. Tice, R.; Costa, D.; Schaich, K., Eds.: Genotoxic Effects of Airborn Agents. New York: Plenum Press, pp. 257-275.

166. Topham, J. (1980) Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? Mutat. Res. 74:379-387.

167. Tucker, M. (1979) Tumours of the Harderian gland. Turusov, V., Ed.: Pathology of Tumours in Laboratory Animals. Vol. II--Tumours of the Mouse. Lyon, France: International Agency for Research on Cancer, pp. 135-145.

168. Tunek, A.; Platt, K.; Bentley, P.; Oesch, F. (1978) Microsomal metabolism of benzene to species irreversibly binding to microsomal protein and effects of modifications of this metabolism. Mol. Pharmacol. 14:920-929.

169. Tunek, A.; Platt, K.; Przybylski, M.; Oesch, F. (1980) Multi-step metabolic activation of benzene. Effect of superoxide dismutase on covalent binding to microsomal macromolecules, and identification of glutathione conjugates using high pressure liquid chromatography and field desorption mass spectrometry. Chem.-Biol. Interact. 33:1-17.

170. Tunek, A.; Hogstedt, B.; Olofsson, T. (1982) Mechanism of benzene toxcity. Effects of benzene and benzene metabolites on bone marrow cellularity, number of granulopoietic stem cells and frequency of micronuclei in mice. Chem.-Biol. Interact. 39:129-138.

171. Umeda, M. (1957) Production of rat sarcoma by injections of propylene glycol solution of *p*-quinone. Gann 48:139-144.

172. Uyeki, E.; El Ashkar, A.; Shoeman, D.; Bisel, T. (1977) Acute toxicity of benzene inhalation to hemopoietic precursor cells. Toxicol. Appl. Pharmacol. 40:49-57.

173. Van Duuren, B.; Goldschmidt, B. (1976) Cocarcinogenic and tumor-promoting agents in tobacco carcinogenesis. J. Natl. Cancer Inst. 56:1237-1242.

174. Van Duuren, B.; Sivak, A.; Langseth, L.; Goldschmidt, B.; Segal, A. (1968) Initiators and Promoters in Tobacco Carcinogenesis. Toward a Less Harmful Cigarette. National Cancer Institute Monograph 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Cancer Institute, pp. 173-180.

175. Van Duuren, B.; Katz, C.; Goldschmidt, B. (1973) Brief communication: Cocarcinogenic agents in tobacco carcinogenesis. J. Natl. Cancer Inst. 51:703-705.

176. Van Raalte, H.; Grasso, P. (1982) Hematological, myelotoxic, clastogenic, carcinogenic, and leukemogenic effects of benzene. Regul. Toxicol. Pharmacol. 2:153-176.

177. Vigliani, E. (1976) Leukemia associated with benzene exposure. Ann. N.Y. Acad. Sci. 271:143-151.

178. Watanabe, G.-I.; Yoshida, S. (1970) The teratogenic effect of benzene in pregnant mice. Acta Med. Biol. (Niigata) 17(1):285-291.

179. Wild, D.; King, M.-T.; Eckhardt, K.; Gocke, E. (1981) Mutagenic activity of aminophenols and diphenols, and relations with chemical structure. Mutat. Res. 85:456.

180. Winer, B. (1971) Statistical Principles in Experimental Design. New York: McGraw-Hill, pp. 518-539.

181. Wolf, M.; Rowe, V.; McCollister, D.; Hollingsworth, R.; Oyen, F. (1956) Toxicological studies of certain alkylated benzenes and benzene. AMA Arch. Ind. Health 14:387-398.

182. Wynder, E.; Hoffmann, D. (1961) A study of tobacco carcinogenesis. VIII. The role of the acidic fractions as promoters. Cancer 14:1306-1315.

183. Yahagi, T.; Degawa, M.; Seino, Y.; Matsushima, T.; Nagao, M.; Sugimura, T.; Hashimoto, Y. (1975) Mutagenicity of carcinogenic azo dyes and their derivatives. Cancer Lett. 1:91-96.

184. Yunis, J. (1983) The chromosomal basis of human neoplasia. Science 221:227-236.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
UNDIFFERENTIATED CARCINOMA				1 (2%)
SQUAMOUS CELL PAPILLOMA		2 (4%)	1 (2%)	5 (10%)
SQUAMOUS CELL CARCINOMA		5 (10%)	3 (6%)	†8 (16%)
TRICHOEPITHELIOMA		3 (6%)	1 (2%)	1 (2%)
SEBACEOUS ADENOMA		3 (6%)	2 (4%)	
ADENOSQUAMOUS CARCINOMA	1 (2%)		1 (2%)	
KERATOACANTHOMA	2 (4%)		1 (2%)	
FIBROSARCOMA			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, INVASIVE				1 (2%)
SQUAMOUS CELL CARCINOMA, METASTATIC				1 (2%)
FIBROMA	4 (8%)	2 (4%)	3 (6%)	4 (8%)
FIBROSARCOMA	1 (2%)	1 (2%)	1 (2%)	3 (6%)
FIBROUS HISTIOCYTOMA, MALIGNANT			1 (2%)	
LIPOMA				1 (2%)
OSTEOSARCOMA		1 (2%)		
NEUROFIBROMA	1 (2%)			
NEUROFIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(49)	(50)
CARCINOMA, NOS, METASTATIC	1 (2%)	1 (2%)	1 (2%)	2 (4%)
SQUAMOUS CELL CARCINOMA		1 (2%)		
SQUAMOUS CELL CARCINOMA, METASTATIC		1 (2%)	2 (4%)	4 (8%)
ADENOCARCINOMA, NOS, METASTATIC			2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
C-CELL CARCINOMA, METASTATIC			1 (2%)	
CARCINOSARCOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	7 (14%)	2 (4%)	4 (8%)	6 (12%)
#MANDIBULAR L. NODE	(42)	(37)	(34)	(37)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	1 (3%)
#CERVICAL LYMPH NODE	(42)	(37)	(34)	(37)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
#THYMUS	(44)	(42)	(41)	(34)
THYMOMA	1 (2%)			
CIRCULATORY SYSTEM				
#SPLEEN	(49)	(48)	(47)	(47)
HEMANGIOSARCOMA		1 (2%)		
#THYMIC LYMPH NODE	(42)	(37)	(34)	(37)
HEMANGIOSARCOMA		1 (3%)		
#HEART	(50)	(49)	(49)	(50)
CARCINOSARCOMA, METASTATIC			1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
*MOUTH/ORAL CAVITY	(50)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)		
*PALATE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		4 (8%)	4 (8%)	9 (18%)
SQUAMOUS CELL CARCINOMA			1 (2%)	
*LIP	(50)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)		
SQUAMOUS CELL PAPILLOMA		2 (4%)	5 (10%)	5 (10%)
SQUAMOUS CELL CARCINOMA				3 (6%)
*TONGUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		2 (4%)	2 (4%)
SQUAMOUS CELL CARCINOMA		3 (6%)	4 (8%)	4 (8%)
#SALIVARY GLAND	(49)	(49)	(47)	(49)
CARCINOMA, NOS, UNC PRIM OR META				1 (2%)
SQUAMOUS CELL CARCINOMA, INVASIVE				1 (2%)
#LIVER	(50)	(48)	(49)	(49)
NEOPLASTIC NODULE	2 (4%)	2 (4%)	4 (8%)	1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)	
#PANCREAS	(49)	(44)	(47)	(49)
ACINAR-CELL ADENOMA	5 (10%)	1 (2%)	3 (6%)	
#CARDIAC STOMACH	(48)	(44)	(48)	(47)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
#JEJUNUM	(44)	(42)	(45)	(44)
ADENOCARCINOMA, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY/CORTEX	(50)	(48)	(48)	(48)
TUBULAR-CELL ADENOCARCINOMA	1 (2%)			
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(45)	(46)	(48)
CARCINOMA, NOS	4 (9%)			
CARCINOMA, NOS, INVASIVE		1 (2%)		
ADENOMA, NOS	14 (30%)	11 (24%)	11 (24%)	7 (15%)
#ADRENAL	(50)	(49)	(48)	(49)
PHEOCHROMOCYTOMA	11 (22%)	11 (22%)	5 (10%)	4 (8%)
#THYROID	(49)	(47)	(46)	(47)
CARCINOMA, NOS, METASTATIC		1 (2%)		
FOLLICULAR-CELL ADENOMA				2 (4%)
FOLLICULAR-CELL CARCINOMA	1 (2%)		2 (4%)	1 (2%)
C-CELL ADENOMA	7 (14%)	4 (9%)	1 (2%)	2 (4%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	3 (7%)	
#PARATHYROID	(33)	(38)	(37)	(44)
ADENOMA, NOS			1 (3%)	
#PANCREATIC ISLETS	(49)	(44)	(47)	(49)
ISLET-CELL ADENOMA		1 (2%)	1 (2%)	
ISLET-CELL CARCINOMA	1 (2%)		2 (4%)	2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)			
FIBROADENOMA	1 (2%)			
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)	1 (2%)		
SQUAMOUS CELL CARCINOMA		1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#TESTIS	(50)	(48)	(50)	(48)
INTERSTITIAL-CELL TUMOR	34 (68%)	37 (77%)	34 (68%)	32 (67%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(49)	(50)	(48)	(48)
CARCINOMA, NOS, METASTATIC			1 (2%)	1 (2%)
GRANULAR-CELL TUMOR, BENIGN		2 (4%)		
#CEREBRUM	(49)	(50)	(48)	(48)
GRANULAR-CELL TUMOR, BENIGN			1 (2%)	
ASTROCYTOMA			1 (2%)	
#PONS	(49)	(50)	(48)	(48)
CARCINOMA, NOS, INVASIVE	1 (2%)			
#MEDULLA OBLONGATA	(49)	(50)	(48)	(48)
CARCINOMA, NOS, INVASIVE		1 (2%)		
SPECIAL SENSE ORGANS				
*EYELID	(50)	(50)	(50)	(50)
SEBACEOUS ADENOMA			1 (2%)	
#HARDERIAN GLAND	(49)	(49)	(49)	(50)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS			1 (2%)	
*EXTERNAL EAR	(50)	(50)	(50)	(50)
FIBROSARCOMA		1 (2%)		
#ZYMBAL GLAND	(32)	(46)	(42)	(42)
CARCINOMA, NOS	2 (6%)	6 (13%)	10 (24%)	17 (40%)
ADENOMA, NOS		1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
CARCINOSARCOMA, INVASIVE			1 (2%)	
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
FIBROSARCOMA				1 (2%)
*PLEURA	(50)	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)			
*TUNICA VAGINALIS	(50)	(50)	(50)	(50)
MESOTHELIOMA, NOS	3 (6%)	1 (2%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS				
DIAPHRAGM				
ADENOCARCINOMA, NOS, METASTATIC			1	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	4	10	7	11
MORIBUND SACRIFICE	8	8	13	19
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	32	29	24	16
DOSING ACCIDENT	3	2	5	4
ACCIDENTALLY KILLED, NOS	3	1	1	
ANIMAL MISSING				
ANIMAL MISSEXED				
OTHER CASES				

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

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	44	48	49	48
TOTAL PRIMARY TUMORS	110	115	121	126
TOTAL ANIMALS WITH BENIGN TUMORS	40	41	42	42
TOTAL BENIGN TUMORS	82	86	77	75
TOTAL ANIMALS WITH MALIGNANT TUMORS	20	24	30	37
TOTAL MALIGNANT TUMORS	23	26	38	48
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	3	7	8
TOTAL SECONDARY TUMORS	2	7	12	11
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	5	3	5	2
TOTAL UNCERTAIN TUMORS	5	3	6	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				1
TOTAL UNCERTAIN TUMORS				1

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN. TISSUE IS COUNTED ONCE ONLY.

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		1 (2%)	
SQUAMOUS CELL CARCINOMA				1 (2%)
KERATOACANTHOMA			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
FIBROMA	2 (4%)			1 (2%)
LIPOSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC	1 (2%)			3 (6%)
CARCINOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	6 (12%)	7 (14%)	6 (12%)	9 (18%)
#CERVICAL LYMPH NODE	(48)	(42)	(43)	(39)
C-CELL CARCINOMA, METASTATIC		1 (2%)		
CIRCULATORY SYSTEM				
#RIGHT VENTRICLE	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC				1 (2%)
DIGESTIVE SYSTEM				
*PALATE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	3 (6%)	5 (10%)	3 (6%)
SQUAMOUS CELL CARCINOMA		1 (2%)		1 (2%)
*LIP	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			2 (4%)	2 (4%)
*TONGUE	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)	
SQUAMOUS CELL CARCINOMA			4 (8%)	4 (8%)
#LIVER	(50)	(49)	(50)	(50)
NEOPLASTIC NODULE		3 (6%)	1 (2%)	
#CARDIAC STOMACH	(50)	(50)	(48)	(49)
SQUAMOUS CELL PAPILLOMA				1 (2%)
#JEJUNUM	(50)	(48)	(47)	(48)
LEIOMYOSARCOMA		1 (2%)		
#COLON	(48)	(49)	(45)	(48)
ADENOMATOUS POLYP, NOS		1 (2%)		
URINARY SYSTEM				
NONE				

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR *GAVAGE* STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(50)	(48)	(49)
CARCINOMA, NOS, INVASIVE		1 (2%)		
ADENOMA, NOS	22 (47%)	15 (30%)	15 (31%)	8 (16%)
#ADRENAL	(50)	(50)	(47)	(49)
CORTICAL ADENOMA	1 (2%)			1 (2%)
PHEOCHROMOCYTOMA	2 (4%)	1 (2%)	2 (4%)	1 (2%)
#THYROID	(50)	(50)	(50)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)	2 (4%)	2 (4%)	
FOLLICULAR-CELL CARCINOMA		2 (4%)	2 (4%)	
C-CELL ADENOMA	1 (2%)	4 (8%)	4 (8%)	1 (2%)
C-CELL CARCINOMA	3 (6%)	3 (6%)	1 (2%)	2 (4%)
#PANCREATIC ISLETS	(49)	(50)	(49)	(49)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS	2 (4%)		2 (4%)	
FIBROADENOMA	10 (20%)	14 (28%)	10 (20%)	4 (8%)
*CLITORAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)			3 (6%)
*VAGINA	(50)	(50)	(50)	(50)
FIBROMA	1 (2%)			
#UTERUS	(50)	(50)	(49)	(50)
SARCOMA, NOS		1 (2%)		
LEIOMYOMA	1 (2%)			
ENDOMETRIAL STROMAL POLYP	7 (14%)	7 (14%)	7 (14%)	14 (28%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)			
#CERVIX UTERI	(50)	(50)	(49)	(50)
ADENOSQUAMOUS CARCINOMA			1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)	(50)
CARCINOMA, NOS		2 (4%)		
ADENOMA, NOS		1 (2%)		
ADENOCARCINOMA, NOS			2 (4%)	2 (4%)
#OVARY	(50)	(50)	(49)	(50)
GRANULOSA-CELL TUMOR			2 (4%)	
NERVOUS SYSTEM				
#CEREBRUM	(50)	(50)	(50)	(50)
ASTROCYTOMA				1 (2%)
#BRAIN	(50)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE		1 (2%)		
SPECIAL SENSE ORGANS				
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
CARCINOMA, NOS, INVASIVE			1 (2%)	
*EAR CANAL	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
#ZYMBAL GLAND	(45)	(40)	(44)	(46)
CARCINOMA, NOS		5 (13%)	5 (11%)	14 (30%)
ADENOMA, NOS			1 (2%)	1 (2%)
CARCINOSARCOMA			1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	1	2	5	4
MORIBUND SACRIFICE	3	8	10	16
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	46	38	33	25
DOSING ACCIDENT		2	2	5
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	38	39	41	42
TOTAL PRIMARY TUMORS	66	76	80	74
TOTAL ANIMALS WITH BENIGN TUMORS	35	30	32	25
TOTAL BENIGN TUMORS	52	51	52	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	19	23	30
TOTAL MALIGNANT TUMORS	14	22	25	37
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	2	3
TOTAL SECONDARY TUMORS	1	3	2	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		3	3	
TOTAL UNCERTAIN TUMORS		3	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
##SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	041	104	025	012	104	104	104	104	104	104	104	104	104	104	059	104	104	104	104	104	101	096	087	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenosquamous carcinoma																							X		
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X				X	X								
Fibrosarcoma																									
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	–
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Thymoma, benign																						X			
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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															X										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					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							X	X		X															
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Small intestine	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular-cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X													X		
Adenoma, NOS						X	X					X													
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma							X										X	X			X	X			X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																						X			
C cell adenoma									X	X		X					X		X					X	
C-cell carcinoma																									
Parathyroid	–	+	+	+	+	+	+	+	–	–	+	+	–	–	+	+	+	+	–	+	–	–	–	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	N	N	+	N	+	N	N	+	N	+	N	N	N	N	+	+	+	+	+	N	+
Adenoma, NOS									X																
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Interstitial-cell tumor		X			X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Carcinoma, NOS													X												
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
Osteosarcoma												X													
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	N	N
Leukemia, mononuclear cell			X																X		X	X			

\+ Tissue examined microscopically
– Required tissue not examined microscopically
N Necropsy, no autolysis, no microscopic examination
X Tumor incidence
No tissue information submitted

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

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
WEEKS ON STUDY	104	104	083	104	104	104	104	074	104	104	059	068	104	088	104	031	029	104	032	104	046	047	048	035	083	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50*	
Adenosquamous carcinoma																									1	
Keratoacanthoma												X							X						2	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	50*	
Fibroma																						X			4	
Fibrosarcoma												X													1	
Neurofibroma									X																1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS, metastatic														X											1	
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph nodes	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	42	
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	–	+	+	44	
Thymoma, benign																									1	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
Squamous cell papilloma																									1	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Neoplastic nodule																			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												5	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49	
Stomach	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	44	
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Tubular-cell adenocarcinoma														X											1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	47	
Carcinoma, NOS																					X	X			4	
Adenoma, NOS		X	X		X		X	X	X				X					X	X		X			X	14	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma		X		X						X			X								X				11	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49	
Follicular-cell carcinoma																									1	
C-cell adenoma									X																7	
C-cell carcinoma		X						X																	2	
Parathyroid	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	–	–	+	–	–	+	+	+	–	+	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Islet-cell carcinoma																									1	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	+	+	+	N	N	+	N	+	+	+	+	N	+	+	+	+	N	+	+	N	50*
Adenoma, NOS						X																			1	
Fibroadenoma																									1	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Interstitial-cell tumor	X	X	X	X	X	X	X			X			X	X	X			X	X		X	X			34	
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*	
Carcinoma, NOS																			X						2	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, NOS, invasive																						X			1	
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49	
Zymbal gland	–	–	–	–	+	+	–	+	–	+	–	+	–	+	+	–	+	–	+	–	+	–	+	–	32	
Carcinoma, NOS														X											2	
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	50*	
Osteosarcoma																									1	
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*	
Mesothelioma, NOS			X		X																				3	
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*	
Leukemia, mononuclear cell			X														X					X			7	

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	068	104	104	050	090	100	104	043	104	080	102	104	104	104	095	100	102	089	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma												X													
Trichoepithelioma																									
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma						X																			
Osteosarcoma																X									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic															X										
Squamous cell carcinoma										X															
Squamous cell carcinoma, metastatic												X													
Trachea	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Lymph nodes	–	+	+	+	+	+	+	+	+	–	–	+	–	–	+	+	–	+	+	+	+	–	+	+	+
Hemangiosarcoma																			X						
Thymus	–	+	–	+	+	–	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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, invasive															X				X						
Squamous cell papilloma												X									X				
Squamous cell carcinoma	X			X							X														
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Neoplastic nodule																			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														X											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Small intestine	+	+	+	–	–	+	+	+	+	+	+	–	+	+	–	–	–	+	+	+	+	+	+	+	+
Large intestine	+	+	+	–	–	+	+	+	+	+	–	+	+	+	–	–	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	–	+	+	+	+	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive															X										
Adenoma, NOS		X			X		X						X					X	X				X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X			X		X		X			X				X			X						
Thyroid	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic															X										
C-cell adenoma							X							X					X						
C-cell carcinoma																									
Parathyroid	+	+	+	–	+	+	+	+	+	+	–	–	+	+	–	+	–	+	–	+	+	+	+	+	+
Pancreatic islets	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	N	+	+	+	N	+	+	+	+	N	N	+	N	+	N	+	+	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor			X		X	X			X	X		X	X	X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
Squamous cell carcinoma																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive															X										
Granular-cell tumor, benign																									
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Ear	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																							X		
Zymbal gland	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS			X												X					X					
Adenoma, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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
Leukemia, mononuclear cell							X																		

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	1001	1004	1004	0555	0899	0996	1004	1004	1004	1004	1000	1004	1004	0771	1004	1004	0355	1004	0808	0559	0665	1004	1004	1004	1004	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma							X	X																		2
Squamous cell carcinoma			X		X						X													X		5
Trichoepithelioma																X		X						X		3
Sebaceous adenoma						X	X			X																3
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma						X			X																	2
Fibrosarcoma																										1
Osteosarcoma																										1
Neurofibrosarcoma								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic																										1
Squamous cell carcinoma																										1
Squamous cell carcinoma, metastic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	+	–	+	–	+	+	37
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS, invasive																										2
Squamous cell papilloma						X						X						X				X				6
Squamous cell carcinoma																										3
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	44
Acinar-cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	44
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Carcinoma, NOS, invasive																										1
Adenoma, NOS											X				X								X			11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma					X			X			X												X			11
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS, metastatic																										1
C-cell adenoma																							X			4
C-cell carcinoma					X																					1
Parathyroid	+	+	–	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	–	–	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	44
Islet-cell adenoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	+	+	+	+	N	+	+	N	N	+	N	N	N	N	N	N	N	+	+	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial-cell tumor	X	X	X		X	X	X	X	X	X		X	X		X	X		X		X		X	X	X	X	37
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	46
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Granular-cell tumor, benign												X		X												2
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS												X														1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma																										1
Zymbal gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS				X										X							X					6
Adenoma, NOS																X										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Mesothelioma, NOS																									X	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leukemia, mononuclear cell	X																									2

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: MID DOSE

ANIMAL NUMBER	00101	00102	00103	00104	00105	00106	00907	00108	00109	00110	00111	00112	00113	00114	00115	00116	00117	00118	00119	00120	00121	00122	00123	00124	00125
WEEKS ON STUDY	10104	08707	07202	10404	10404	10407	07303	05101	10404	10404	06909	08101	10404	10403	08301	07707	10404	10404	10404	10404	10401	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Squamous cell carcinoma																									
Trichoepithelioma														X											
Sebaceous adenoma										X							X								
Adenosquamous carcinoma																									
Keratoacanthoma																									
Fibrosarcoma																	X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																			X		
Fibrosarcoma																									
Fibrous histiocytoma, malignant																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Squamous cell carcinoma, metastatic																									
Adenocarcinoma, NOS, metastatic																									
C cell carcinoma, metastatic														X											
Carcinosarcoma																									
Trachea	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	–	–	+	–	+	–	+	+	–	–	+	–	+	+	–	+	+	+	+
Squamous cell carcinoma, metastatic																									
Thymus	–	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma, metastatic																									
DIGESTIVE SYSTEM																									
Oral cavity	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					X	X												X		X					X
Squamous cell carcinoma		X										X													
Salivary gland	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule				X					X						X								X		
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	N	N
Pancreas	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma														X			X				X				
Esophagus	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X													X					X
Adrenal	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X				X					X	X					X				
Thyroid	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma				X																	X				
C-cell adenoma																									
C-cell carcinoma														X			X								
Parathyroid	+	+	+	+	+	–	–	–	+	–	+	+	–	+	–	–	–	+	+	+	+	–	+	+	+
Adenoma, NOS																					X				
Pancreatic islets	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																						X			
Islet-cell carcinoma																						X			
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	N	+	N	N	N	N	N	N	+	N	N	N	N	N	+	+	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X		X	X	X	X			X	X	X		X	X	X		X	X		X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Granular-cell tumor, benign																				X					
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Eye appendages	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
Sebaceous adenoma					X																				
Harderian gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Zymbal gland	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Carcinoma, NOS					X	X					X				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	N
Carcinosarcoma, invasive																									
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	N	N
Leukemia, mononuclear cell	X																			X					
Diaphragm, NOS																									
Adenocarcinoma, NOS, metastatic																									

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

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
WEEKS ON STUDY	104	104	100	104	104	097	093	083	073	057	092	080	092	104	098	072	088	104	094	088	104	070	094	086	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma																										1
Squamous cell carcinoma			X			X																		X		3
Trichoepithelioma																										1
Sebaceous adenoma																										2
Adenosquamous carcinoma				X																						1
Keratoacanthoma														X												1
Fibrosarcoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma		X																								3
Fibrosarcoma																		X								1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic													X													1
Squamous cell carcinoma, metastatic			X			X																				2
Adenocarcinoma, NOS, metastatic																		X		X						2
C-cell carcinoma, metastatic																										1
Carcinosarcoma									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	–	–	+	+	–	+	–	+	–	+	34
Squamous cell carcinoma, metastatic			X			X																				2
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinosarcoma, metastatic									X																	1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell papilloma	X									X							X	X	X		X					11
Squamous cell carcinoma		X		X												X										5
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																										4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Acinar-cell adenoma																										3
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	45
Adenocarcinoma, NOS																		X								1
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS	X		X	X			X			X			X									X		X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma																										5
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular-cell carcinoma																										2
C-cell adenoma															X											1
C-cell carcinoma						X																				3
Parathyroid	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	–	+	+	+	37
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet-cell adenoma																										1
Islet-cell carcinoma			X																							2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	N	+	N	+	+	N	+	+	N	+	N	N	N	N	N	N	+	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor	X	X	X	X	X	X			X					X	X		X	X	X	X	X						34
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS, metastatic													X													1
Granular-cell tumor, benign																										1
Astrocytoma																				X						1
SPECIAL SENSE ORGANS																										
Eye appendages	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*
Sebaceous adenoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																				X						1
Zymbal gland	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	42
Carcinoma, NOS							X				X	X	X		X									X		10
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	N	50*
Carcinosarcoma, invasive									X																	1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Mesothelioma, NOS	X																									2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leukemia, mononuclear cell															X						X					4
Diaphragm, NOS																										
Adenocarcinoma, NOS, metastatic																		X								1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	104	104	086	104	094	099	088	099	089	104	104	083	104	104	085	104	086	092	094	104	064	104	091	095	087
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																									
Squamous cell papilloma									X							X						X			
Squamous cell carcinoma		X							X																
Trichoepithelioma															X										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic														X											
Fibroma																									
Fibrosarcoma																				X					
Lipoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Squamous cell carcinoma, metastatic		X			X								X												
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	+	+	–	+	–	–	+	–	+	–	–	+	+	+	+	+	+	+	+	+	–
Squamous cell carcinoma, metastatic													X												
Thymus	+	+	–	–	–	+	+	+	–	+	–	–	+	–	–	+	+	+	+	+	+	+	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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				X@		X												X		X		X	X@		
Squamous cell carcinoma													X	X											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Carcinoma, NOS, unc prim or metasta										X															
Squamous cell carcinoma, invasive														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	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	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X																			X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X						X														X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma		X																							
Follicular-cell carcinoma																									
C-cell adenoma		X						X																	
Parathyroid	+	–	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma														X											
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	+	+	N	N	+	+	N	+	N	N	N	+	N	+	+	+	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Interstitial-cell tumor	X	X		X	X		X	X		X	X		X	X		X				X		X	X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Carcinoma, NOS						X	X	X			X	X					X		X	X		X	X		X
Adenoma, NOS																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma								X																	
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Mesothelioma, NOS											X														
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell								X	X							X		X						X	

@ Multiple occurrence of morphology

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

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
WEEKS ON STUDY	090	098	102	104	087	084	095	094	087	095	104	091	083	102	104	100	074	097	104	075	085	091	051	104		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+		50*
Undifferentiated carcinoma		X																								1
Squamous cell papilloma					X															X						5
Squamous cell carcinoma	X@			X					X			X		X							X					8
Trichoepithelioma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+		50*
Squamous cell carcinoma, invasive												X														1
Squamous cell carcinoma, metastatic																										1
Fibroma				X								X								X	X					4
Fibrosarcoma	X																					X				3
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, NOS, metastatic									X											X						2
Squamous cell carcinoma, metastatic																					X					4
Alveolar/bronchiolar carcinoma				X																						1
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Spleen	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Lymph nodes	+	–	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+		37
Squamous cell carcinoma, metastatic																										1
Thymus	+	–	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	–	+		34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Squamous cell papilloma	X	X			X		X								X					X@				X		13
Squamous cell carcinoma									X			X			X	X							X			7
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, NOS, unc prim or metastat																										1
Squamous cell carcinoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		49
Stomach	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		47
Small intestine	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–		44
Large intestine	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Urinary bladder	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+		44
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma, NOS									X						X			X	X							7
Adrenal	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pheochromocytoma											X															4
Thyroid	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		47
Follicular-cell adenoma							X																			2
Follicular-cell carcinoma																			X							1
C-cell adenoma																										2
Parathyroid	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+		44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Islet-cell carcinoma																X										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	N	N	+	+	N	N	N	+	+	+	N	+	+	N	+	N	N	N	N		50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		48
Interstitial-cell tumor	X	X	X	X	X	X	X	X	X			X				X	X	X	X	X	X			X		32
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+		48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+		48
Carcinoma, NOS, metastatic										X																1
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Zymbal gland	–	+	–	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+		42
Carcinoma, NOS									X	X						X			X			X		X		17
Adenoma, NOS													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*
Fibrosarcoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+		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*
Leukemia, mononuclear cell																		X								6

* Animals necropsied
@ Multiple occurrence of morphology

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: 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	104	104	097	104	104	104	104	104	104	104	104	104	104	104	104	104	093	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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															X										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
Adenoma, NOS		X	X	X					X	X		X	X		X							X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma				X																					
Pheochromocytoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																				X					
C-cell adenoma																									
C cell carcinoma					X						X														
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	+	–	–	–	+	+	+	+	+	+	–	–	+	+
Pancreatic islets	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	N	+	+	+	+	N	+	+
Adenocarcinoma, NOS		X		X																					
Fibroadenoma		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
Carcinoma, NOS										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
Fibroma				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp						X				X						X	X		X						
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X																					X		

+ Tissue examined microscopically
– Required tissue not examined microscopically
N Necropsy, no autolysis, no microscopic examination
No tissue information submitted
X Tumor incidence

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

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
WEEKS ON STUDY	104	104	104	104	104	104	104	103	104	104	104	104	033	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma																								X		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma																				X						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X			X	X		X	X	X							X	X	X	X			X	X	X	22
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																							X			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma	X																									2
C-cell adenoma							X																			1
C-cell carcinoma										X																3
Parathyroid	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–	–	–	–	+	+	–	+	+	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	+	N	+	+	+	+	N	N	+	+	N	+	N	+	+	+	N	+	+	+	N	50*
Adenocarcinoma, NOS																										2
Fibroadenoma								X	X	X																10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																										2
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	50*
Fibroma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma											X															1
Endometrial stromal polyp												X													X	7
Endometrial stromal sarcoma										X																1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal gland	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leukemia, mononuclear cell		X							X									X		X						6

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	104	104	104	089	104	104	104	104	104	104	104	078	104	104	104	081	104	103	103	104	104	104	097	084	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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															X					X					
Squamous cell carcinoma																			X						
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Neoplastic nodule	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	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma			X																						
Large intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS		X																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive												X													
Adenoma, NOS				X						X			X	X					X				X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																									
Follicular-cell carcinoma																									
C-cell adenoma															X				X						
C-cell carcinoma	X																					X			
Parathyroid	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	N	N	+	+	+	N	+	+	+	+	+	N	+	+	+	+	N	+	N	+
Adenoma, NOS	X																								
Fibroadenoma				X						X			X	X	X			X		X		X		X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																	X			X					
Adenoma, NOS																									
Sarcoma, NOS																									
Endometrial stromal polyp	X																X		X	X			X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive												X													
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Zymbal gland	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	–	+	+	–	+
Carcinoma, NOS										X		X						X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell							X									X						X	X		

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0262	0272	0289	0301	0312	0323	0334	0345	0367	0378	0399	0401	0411	0423	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	1040	1040	1040	1040	0955	0880	1040	0888	1040	1040	1040	1040	1040	0880	1040	1040	0669	1040	1040	1040	1040	TISSUES TUMORS
RESPIRATORY SYSTEM																						
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
HEMATOPOIETIC SYSTEM																						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	–	+	+	–	+	42
C-cell carcinoma, metastatic											X											1
Thymus	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																						
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell papilloma		X	X																			4
Squamous cell carcinoma																						1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																						3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenomatous polyp, NOS																						1
URINARY SYSTEM																						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																						
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																						1
Adenoma, NOS		X		X	X					X		X				X	X	X			X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma												X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma	X						X															2
Follicular-cell carcinoma											X							X				2
C-cell adenoma			X										X									4
C-cell carcinoma												X										3
Parathyroid	+	+	+	–	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma																						1
REPRODUCTIVE SYSTEM																						
Mammary gland	N	N	+	+	+	N	+	N	+	N	+	+	+	+	N	N	+	+	N	N	+	+	N	N	50*
Adenoma, NOS																						1
Fibroadenoma				X			X				X			X						X		14
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																						2
Adenoma, NOS													X									1
Sarcoma, NOS							X															1
Endometrial stromal polyp								X											X			7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																						1
SPECIAL SENSE ORGANS																						
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal gland	+	+	+	+	+	~	+	+	–	+	+	+	+	+	+	+	+	–	–	–	+	+	+	40
Carcinoma, NOS												X		X								5
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	50*
Leukemia, mononuclear cell						X						X		X								7

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: MID 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	104	104	102	104	096	104	103	104	104	066	104	104	104	104	104	104	069	104	104	104	104	071	082	075	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma														X											
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	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						X		X			X			X						X			X		
Squamous cell carcinoma			X		X												X								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																				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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X		X					X				X		X		X	X			X	X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Pheochromocytoma			X																						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																				X					
Follicular-cell carcinoma												X				X									
C-cell adenoma											X			X											
C-cell carcinoma																									
Parathyroid	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma	X	X										X						X		X					X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Adenosquamous carcinoma																									
Endometrial stromal polyp								X									X	X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-cell tumor																	X		X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																							X		
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Zymbal gland	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+	+
Carcinoma, NOS																						X	X		
Adenoma, NOS														X											
Carcinosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X						X				X			X											

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID DOSE (Continued)

ANIMAL NUMBER	0262	0267	0268	0269	0301	0311	0312	0333	0334	0335	0336	0337	0338	0339	0401	0411	0423	0434	0445	0456	0467	0478	0498	0505	TOTAL
WEEKS ON STUDY	104	104	104	104	104	102	089	072	104	104	052	104	075	104	104	104	104	104	096	104	104	104	041	045	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma																						X			1
Keratoacanthoma																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Liposarcoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinosarcoma, metastatic																			X						1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	44
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell papilloma								X				X													8
Squamous cell carcinoma																							X		4
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																									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	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	45
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Adenoma, NOS				X	X			X	X				X											X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	47
Pheochromocytoma															X										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma									X																2
Follicular-cell carcinoma																									2
C-cell adenoma												X								X					4
C-cell carcinoma																			X						1
Parathyroid	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	–	–	39
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	N	+	N	+	+	+	+	+	N	+	N	+	N	N	+	+	+	+	50*
Adenocarcinoma, NOS								X										X							2
Fibroadenoma												X		X									X		10
Uterus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS										X															2
Adenosquamous carcinoma						X																			1
Endometrial stromal polyp			X											X									X	X	7
Ovary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa-cell tumor																									2
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																									1
Ear	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma																	X								1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, NOS								X	X				X												5
Adenoma, NOS																									1
Carcinosarcoma																			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*
Leukemia, mononuclear cell			X																					X	6

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	075	104	104	104	104	104	097	104	083	075	083	098	057	098	101	002	062	104	104	104	104	087	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Squamous cell carcinoma												X													
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic									X		X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	
Lymph nodes	+	+	+	–	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	–	+	+	+	
Thymus	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	–	+	+	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
DIGESTIVE SYSTEM																									
Oral cavity	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			X					X										X				X			
Squamous cell carcinoma					X									X	X							X			
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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								X																	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Adenoma, NOS				X		X	X											X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
C-cell adenoma				X																					
C-cell carcinoma																					X				
Parathyroid	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	+	N	+	+	N	N	+	+	+	+	+	+	+	+	N	+	N	N	+	N
Fibroadenoma														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											X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Endometrial stromal polyp	X			X		X							X					X		X				X	X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+
Zymbal gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Carcinoma, NOS							X	X	X	X							X		X				X		X
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
Leukemia, mononuclear cell				X								X											X		

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0262	0272	0282	0292	0303	0311	0323	0333	0344	0355	0366	0377	0388	0399	0404	0410	0421	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	1004	0009	0032	1002	1004	1004	1004	1004	1004	0669	1004	1004	0997	1001	1004	0997	0997	1000	1004	1003	1004	0994	0664	1004	1004	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	50*	
Squamous cell carcinoma																									1	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	50*	
Fibroma																X									1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS, metastatic										X															3	
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Lymph nodes	+	+	+	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	39	
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	–	+	+	–	+	+	+	+	+	37	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS, metastatic										X															1	
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*	
Squamous cell papilloma										X															5	
Squamous cell carcinoma																	X								5	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
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	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Squamous cell papilloma																									1	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma, NOS	X		X																	X		X			8	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Cortical adenoma																								X	1	
Pheochromocytoma																X									1	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
C-cell adenoma																									1	
C-cell carcinoma																	X								2	
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	43	
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	N	N	N	+	N	+	N	N	N	N	+	+	N	N	+	N	+	+	N	50*
Fibroadenoma																		X			X					4
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																	X			X						3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenocarcinoma, NOS													X												2	
Endometrial stromal polyp	X												X	X				X						X	X	14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Astrocytoma									X																1	
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Zymbal gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	46	
Carcinoma, NOS	X				X	X				X		X												X	14	
Adenoma, NOS															X										1	
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	X	X	N	X	N	N	N	X	X	X	N	N	N	50*
Leukemia, mononuclear cell																									9	

*Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			2 (4%)	2 (4%)
SQUAM. CELL CARC, UNC PRI OR METAS				1 (2%)
SEBACEOUS ADENOCARCINOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)		2 (4%)
FIBROMA		†1 (2%)		
FIBROSARCOMA	†6 (12%)	4 (8%)	9 (18%)	3 (6%)
NEUROFIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)		1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA				8 (16%)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	1 (2%)	7 (14%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (12%)	6 (12%)	8 (16%)	12 (24%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	11 (22%)	12 (24%)	14 (28%)
RHABDOMYOSARCOMA, METASTATIC				1 (2%)
CARCINOSARCOMA, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	3 (6%)	5 (10%)	6 (12%)	10 (20%)
MALIG. LYMPHOMA, UNDIFFER-TYPE				1 (2%)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		2 (4%)		
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			2 (4%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		
LEUKEMIA, NOS		1 (2%)	1 (2%)	
#SPLEEN	(50)	(50)	(49)	(47)
SARCOMA, NOS, UNC PRIM OR META		1 (2%)		
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)		1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#LYMPH NODE	(43)	(41)	(40)	(37)
SQUAMOUS CELL CARCINOMA, METASTA				1 (3%)
#MANDIBULAR L. NODE	(43)	(41)	(40)	(37)
SQUAMOUS CELL CARCINOMA, METASTA		1 (2%)		
CARCINOSARCOMA, METASTATIC				1 (3%)
#AXILLARY LYMPH NODE	(43)	(41)	(40)	(37)
FIBROSARCOMA, METASTATIC			1 (3%)	
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC	1 (2%)			1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)
#BONE MARROW	(49)	(50)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC				1 (2%)
#SPLEEN	(50)	(50)	(49)	(47)
HEMANGIOSARCOMA				1 (2%)
HEMANGIOSARCOMA, METASTATIC				1 (2%)
*MUSCLE OF LEG	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#HEART	(49)	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)	1 (2%)	
CARCINOSARCOMA, METASTATIC				1 (2%)
#LEFT ATRIUM	(49)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
#LEFT VENTRICLE	(49)	(50)	(50)	(50)
RHABDOMYOSARCOMA				1 (2%)
#LIVER	(50)	(50)	(50)	(48)
HEMANGIOSARCOMA	3 (6%)	1 (2%)	2 (4%)	2 (4%)
HEMANGIOSARCOMA, UNC PRIM OR MET			1 (2%)	
#TESTIS	(50)	(50)	(50)	(48)
HEMANGIOSARCOMA		1 (2%)		
HEMANGIOSARCOMA, UNC PRIM OR MET			1 (2%)	
DIGESTIVE SYSTEM				
*GUM	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
#LIVER	(50)	(50)	(50)	(48)
HEPATOCELLULAR ADENOMA	7 (14%)	11 (22%)	6 (12%)	3 (6%)
HEPATOCELLULAR CARCINOMA	9 (18%)	8 (16%)	17 (34%)	8 (17%)
FIBROSARCOMA, METASTATIC			1 (2%)	
#PANCREAS	(49)	(47)	(48)	(46)
CARCINOSARCOMA		1 (2%)		
#STOMACH	(46)	(44)	(44)	(39)
SQUAMOUS CELL CARCINOMA			1 (2%)	
FIBROSARCOMA			1 (2%)	
#CARDIAC STOMACH	(46)	(44)	(44)	(39)
SQUAMOUS CELL PAPILLOMA	2 (4%)	1 (2%)	2 (5%)	5 (13%)
SQUAMOUS CELL CARCINOMA		1 (2%)		1 (3%)
#GASTRIC FUNDUS	(46)	(44)	(44)	(39)
ADENOCARCINOMA, NOS				1 (3%)
ADENOMATOUS POLYP, NOS		1 (2%)		
#JEJUNUM	(46)	(37)	(40)	(34)
ADENOCARCINOMA, NOS		1 (3%)		1 (3%)
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)	
ALVEOLAR/BRONCHIOLAR CARC, METASTA				1 (2%)
TUBULAR-CELL ADENOMA			1 (2%)	
CARCINOSARCOMA, UNC PRIM OR META				1 (2%)
ENDOCRINE SYSTEM				
#ADRENAL	(48)	(50)	(49)	(47)
CORTICAL ADENOMA				1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	1 (2%)	7 (14%)	1 (2%)
#ADRENAL/CAPSULE	(48)	(50)	(49)	(47)
ADENOMA, NOS		2 (4%)		
#THYROID	(48)	(49)	(49)	(45)
FOLLICULAR-CELL ADENOMA	3 (6%)		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(49)	(47)	(48)	(46)
ISLET-CELL ADENOMA	1 (2%)			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
#PREPUTIAL GLAND	(22)	(28)	(29)	(36)
CARCINOMA, NOS		2 (7%)	1 (3%)	3 (8%)
SQUAMOUS CELL CARCINOMA		3 (11%)	18 (62%)	28 (78%)
CARCINOSARCOMA		1 (4%)		1 (3%)
#TESTIS	(50)	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
SEMINOMA/DYSGERMINOMA		1 (2%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
#HARDERIAN GLAND	(50)	(48)	(49)	(49)
CARCINOMA, NOS	1 (2%)	2 (4%)		3 (6%)
ADENOMA, NOS		9 (19%)	13 (27%)	11 (22%)
MIXED TUMOR, MALIGNANT		1 (2%)		
#ZYMBAL GLAND	(43)	(34)	(40)	(39)
SQUAMOUS CELL CARCINOMA		1 (3%)	4 (10%)	21 (54%)
CARCINOSARCOMA				1 (3%)
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		1 (2%)	
ALVEOLAR/BRONCHIOLAR CARC, METASTA			1 (2%)	2 (4%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)	
SQUAMOUS CELL CARCINOMA, METASTA				2 (4%)
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)		
ALVEOLAR/BRONCHIOLAR CA, METASTA		2 (4%)	1 (2%)	1 (2%)
FIBROSARCOMA, METASTATIC	1 (2%)		2 (4%)	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	14	18	15	20
MORIBUND SACRIFICE	6	7	16	21
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	28	22	18	7
DOSING ACCIDENT	2	3		2
ACCIDENTALLY KILLED, NOS			1	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	33	40	48	45
TOTAL PRIMARY TUMORS	49	84	118	148
TOTAL ANIMALS WITH BENIGN TUMORS	18	25	27	25
TOTAL BENIGN TUMORS	20	33	38	34
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	34	43	45
TOTAL MALIGNANT TUMORS	29	50	78	112
TOTAL ANIMALS WITH SECONDARY TUMORS##	3	6	14	19
TOTAL SECONDARY TUMORS	4	7	17	25
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				
TOTAL UNCERTAIN TUMORS				
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC		1	1	2
TOTAL UNCERTAIN TUMORS		1	2	2

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN. TISSUE IS COUNTED ONCE ONLY.

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)	
SEBACEOUS ADENOMA	1 (2%)			
KERATOACANTHOMA			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)	
FIBROSARCOMA	1 (2%)	4 (8%)	3 (6%)	1 (2%)
OSTEOSARCOMA	1 (2%)			
RESPIRATORY SYSTEM				
#LUNG	(50)	(47)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)	2 (4%)	3 (6%)
CARCINOMA, NOS, UNC PRIM OR META				1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ISLET-CELL CARCINOMA, METASTATIC			1 (2%)	
HEPATOCELLULAR CARCINOMA, METAST		1 (2%)		2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	2 (4%)	5 (10%)	9 (18%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (6%)	6 (12%)	6 (12%)
GRANULOSA-CELL CARCINOMA, METAST				1 (2%)
CARCINOSARCOMA, METASTATIC				1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	13 (26%)	15 (30%)	16 (32%)	13 (26%)
MALIG. LYMPHOMA, UNDIFFER-TYPE		1 (2%)	1 (2%)	1 (2%)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	2 (4%)	2 (4%)	2 (4%)	4 (8%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	3 (6%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		
LEUKEMIA, NOS			2 (4%)	2 (4%)
UNDIFFERENTIATED LEUKEMIA		1 (2%)		
#SPLEEN	(49)	(49)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		2 (4%)	1 (2%)	
MALIG. LYMPHOMA, UNDIFFER-TYPE			1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#RENAL LYMPH NODE	(46)	(43)	(39)	(45)
FIBROSARCOMA, METASTATIC	1 (2%)			
#UTERUS	(50)	(49)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)		
CIRCULATORY SYSTEM				
*PERITONEAL CAVITY	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOMA				1 (2%)
HEMANGIOSARCOMA	1 (2%)			
#SPLEEN	(49)	(49)	(50)	(49)
HEMANGIOSARCOMA			1 (2%)	
#PANCREATIC L. NODE	(46)	(43)	(39)	(45)
HEMANGIOSARCOMA, METASTATIC	1 (2%)			

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#MESENTERIC L. NODE	(46)	(43)	(39)	(45)
HEMANGIOSARCOMA, METASTATIC	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	1 (2%)	8 (16%)	5 (10%)	4 (8%)
HEPATOCELLULAR CARCINOMA	3 (6%)	4 (8%)	8 (16%)	4 (8%)
#STOMACH	(43)	(45)	(45)	(43)
SQUAMOUS CELL PAPILLOMA				1 (2%)
#CARDIAC STOMACH	(43)	(45)	(45)	(43)
SQUAMOUS CELL PAPILLOMA	1 (2%)	3 (7%)	6 (13%)	4 (9%)
#JEJUNUM	(40)	(42)	(44)	(41)
ADENOCARCINOMA, NOS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(49)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)	
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(39)	(45)	(35)
ADENOMA, NOS	13 (28%)	5 (13%)	6 (13%)	4 (11%)
#ADRENAL	(50)	(49)	(50)	(49)
CORTICAL ADENOMA	1 (2%)		1 (2%)	1 (2%)
PHEOCHROMOCYTOMA	6 (12%)	1 (2%)	1 (2%)	1 (2%)
PHEOCHROMOCYTOMA, MALIGNANT	2 (4%)			
#ADRENAL/CAPSULE	(50)	(49)	(50)	(49)
ADENOMA, NOS			3 (6%)	
#THYROID	(49)	(46)	(48)	(47)
FOLLICULAR-CELL ADENOMA	3 (6%)	1 (2%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(47)	(46)	(48)	(43)
ISLET-CELL ADENOMA	1 (2%)			
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS		2 (4%)	5 (10%)	8 (16%)
SQUAMOUS CELL CARCINOMA				2 (4%)
CARCINOSARCOMA			1 (2%)	4 (8%)
#UTERUS	(50)	(49)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)	
LEIOMYOMA				1 (2%)
ENDOMETRIAL STROMAL POLYP	2 (4%)			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)	(50)
ADENOCARCINOMA, NOS				1 (2%)
#OVARY	(48)	(49)	(49)	(49)
PAPILLARY CYSTADENOMA, NOS			2 (4%)	1 (2%)
LUTEOMA		2 (4%)	3 (6%)	2 (4%)
GRANULOSA-CELL TUMOR	1 (2%)	1 (2%)	6 (12%)	7 (14%)
GRANULOSA-CELL CARCINOMA				1 (2%)
TUBULAR ADENOMA			3 (6%)	3 (6%)
MIXED TUMOR, BENIGN		1 (2%)	12 (24%)	7 (14%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY IN BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(50)	(49)
ASTROCYTOMA	1 (2%)			
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
MALIGNANT MELANOMA	1 (2%)			
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
CARCINOMA, NOS				4 (8%)
ADENOMA, NOS	5 (10%)	6 (12%)	10 (20%)	6 (13%)
#ZYMBAL GLAND	(43)	(33)	(37)	(31)
SQUAMOUS CELL CARCINOMA			1 (3%)	3 (10%)
CARCINOSARCOMA				1 (3%)
MUSCULOSKELETAL SYSTEM				
*SKULL	(50)	(50)	(50)	(50)
OSTEOSARCOMA			1 (2%)	
*FEMUR	(50)	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	1 (2%)			
*MUSCLE OF BACK	(50)	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)			
BODY CAVITIES				
*THORACIC CAVITY	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC				1 (2%)
*MEDIASTINUM	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)	
ALVEOLAR/BRONCHIOLAR CARC, METASTA				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC				1 (2%)
SQUAM. CELL CARC, UNC PRI OR METAS				2 (4%)
ADENOCAR, NOS, UNC PRIM OR METASTA			1 (2%)	
SARCOMA, NOS, METASTATIC	1 (2%)			
OSTEOSARCOMA, METASTATIC			1 (2%)	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	10	12	9	17
MORIBUND SACRIFICE	6	8	17	16
SCHEDULED SACRIFICE				
TERMINAL SACRIFICE	30	25	24	16
DOSING ACCIDENT	4			1
ACCIDENTALLY KILLED, NDA		1		
ACCIDENTALLY KILLED, NOS		4		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY IN BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	36	40	48	48
TOTAL PRIMARY TUMORS	65	70	124	115
TOTAL ANIMALS WITH BENIGN TUMORS	23	23	35	26
TOTAL BENIGN TUMORS	38	30	60	47
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	33	38	37
TOTAL MALIGNANT TUMORS	26	39	57	58
TOTAL ANIMALS WITH SECONDARY TUMORS##	4	2	4	9
TOTAL SECONDARY TUMORS	6	2	5	11
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	6	7
TOTAL UNCERTAIN TUMORS	1	1	6	7
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			1	3
TOTAL UNCERTAIN TUMORS			1	3

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	104	104	104	104	086	103	104	104	041	104	104	104	081	104	003	043	104	104	104	041	087	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma		X																						X	
Alveolar/bronchiolar carcinoma	X	X						X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X							X		X					X		X				X		
Hepatocellular carcinoma					X								X						X						
Hemangiosarcoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+
Squamous cell papilloma						X																		X	
Small intestine	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma											X														
Parathyroid	–	–	+	–	+	+	+	–	–	+	–	–	+	–	–	–	+	–	+	+	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	+	+	–	+	+	–	–	+	–	–	+	–	–	–	+	+	–	–	–	+	–	+	+	+	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS														X											
Zymbal gland	–	+	–	+	–	+	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+
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	N
Hepatocellular carcinoma, metastatic																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic																					X				
Hemangiosarcoma, metastatic																								X	
Malignant lymphoma, NOS						X																			

+ : Tissue examined microscopically
– : Required tissue not examined microscopically
X : tumor incidence
N : Necropsy, no autolysis, No microscopic examination
: No tissue information submitted

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0262	0273	0282	0292	0303	0311	0323	0333	0344	0355	0366	0377	0388	0399	0401	0411	0422	0433	0444	0455	0466	0477	0488	0499	0501	TOTAL
WEEKS ON STUDY	1102	1036	1022	0822	1022	1044	1033	1044	0999	1044	1044	1044	0777	0559	1044	0885	0993	1049	1099	1044	0992	1049	0973	1044	1044	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma			X	X	X	X			X@																	6
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic	X																									1
Alveolar/bronchiolar adenoma								X											X		X	X				6
Alveolar/bronchiolar carcinoma									X								X									5
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS										X																1
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	43
Thymus	–	+	–	+	–	–	–	+	–	–	+	+	+	+	+	–	–	+	+	+	–	+	–	+	–	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X																		7
Hepatocellular carcinoma	X			X												X	X		X		X					9
Hemangiosarcoma							X						X													3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	N	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	46
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma									X																	1
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular-cell adenoma																				X					X	3
Parathyroid	–	–	–	–	–	+	+	–	+	+	–	+	+	–	–	+	+	–	–	–	–	–	–	–	–	21
Pancreatic islets	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell adenoma																	X									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	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	+	–	–	–	+	+	–	+	–	–	–	+	+	–	+	–	+	–	–	–	–	–	+	+	–	22
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	43
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	N	50*
Hepatocellular carcinoma, metastatic	X																									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Fibrosarcoma, metastatic																										1
Hemangiosarcoma, metastatic																										1
Malignant lymphoma, NOS				X				X																		3

* Animals necropsied
@ Multiple occurrence of morphology

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	0994	0886	1001	1004	1004	0990	1004	1004	1004	0288	1004	0996	0884	0339	0444	0000	0997	1022	1004	1003	0685	0854	1004	0990	0774
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Fibroma								X@																	
Fibrosarcoma		X										X										X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Hepatocellular carcinoma, metastatic																				X					
Alveolar/bronchiolar adenoma				X													X	X						X	
Alveolar/bronchiolar carcinoma			X			X			X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unc prim or metastatic																									
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	–	–	+	+	–	+	+	–	+	+	–	+
Squamous cell carcinoma, metastatic	X																								
Thymus	–	–	+	–	–	–	+	+	+	+	+	+	+	–	+	–	–	–	+	–	+	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																				X					
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Hepatocellular carcinoma	X																			X		X	X		
Hemangiosarcoma													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	+	N	+	+	+	+	+	N	N	+	N	+	+	N	+	+	+	+	+	+	N
Pancreas	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–
Squamous cell papilloma					X																				
Squamous cell carcinoma																									
Adenomatous polyp, NOS																									
Small intestine	–	+	+	–	+	+	+	+	+	+	+	–	–	–	–	+	+	–	+	+	+	+	+	–	–
Adenocarcinoma, NOS								X																	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X																				
Pheochromocytoma																									
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminoma/dysgerminoma																									
Hemangiosarcoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	–	–	–	+	+	+	+	+	+	–	+	–	–	+	–	–	–	+	+	–	–	–	–	–	+
Carcinoma, NOS									X																
Squamous cell carcinoma																									
Carcinosarcoma																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																				X					
Adenoma, NOS							X				X											X			
Mixed tumor, malignant																									X
Zymbal gland	+	+	–	–	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+
Squamous cell carcinoma	X																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar carcin, metastatic																									
Malignant lymphoma, NOS							X																		
Malig lymphoma, lymphocytic type	X					X																			
Malignant lymphoma, mixed type																									
Leukemia, NOS																									

@ Multiple occurrence of morphology

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

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
WEEKS ON STUDY	103	104	102	104	104	001	104	104	038	104	104	081	104	104	100	104	083	104	104	086	104	101	104	104	097	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS																										1
Fibroma																										1
Fibrosarcoma															X											4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																								X		1
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma											X											X				6
Alveolar/bronchiolar carcinoma		X			X							X					X		X		X	X		X		11
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unc prim or metastatic		X																								1
Malignant lymphoma, NOS																			X							1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	41
Squamous cell carcinoma, metastatic																										1
Thymus	+	+	–	+	–	–	+	+	+	–	–	–	+	+	+	+	–	+	+	+	–	+	+	+	–	+	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X		X	X						X		X	X		X					X	X		X		11
Hepatocellular carcinoma			X		X								X					X								8
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	50*
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinosarcoma																				X						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	44
Squamous cell papilloma																										1
Squamous cell carcinoma		X																								1
Adenomatous polyp, NOS																					X					1
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	37
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																								X		2
Pheochromocytoma																		X								1
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	–	–	–	–	–	–	–	–	–	–	+	+	+	–	+	–	+	+	–	–	+	–	+	+	15
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	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminoma/dysgerminoma													X													1
Hemangiosarcoma																						X				1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	–	+	–	+	+	–	+	+	–	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	–	28
Carcinoma, NOS							X																			2
Squamous cell carcinoma		X		X									X													3
Carcinosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																								X		2
Adenoma, NOS													X		X				X	X				X	X	9
Mixed tumor, malignant																										1
Zymbal gland	+	+	+	+	+	–	–	–	+	–	+	–	+	–	+	+	–	–	+	+	+	+	–	+	–	34
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Hepatocellular carcinoma, metastatic			X																							1
Alveolar/bronchiolar carcin, metastatic												X										X				2
Malignant lymphoma, NOS				X										X									X		X	5
Malig. lymphoma, lymphocytic type																										2
Malignant lymphoma, mixed type	X																									1
Leukemia, NOS																					X					1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: MID DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	1004	1004	1004	1004	0777	0666	1003	1001	0888	0995	0887	1003	0999	1000	0994	1004	1004	1004	0991	1004	1004	0885	0842	0229	0977	097
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibrosarcoma			X			X						X													X
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic								X							X						X			X	
Alveolar/bronchiolar adenoma					X			X	X					X		X				X					
Alveolar/bronchiolar carcinoma	X	X			X							X			X			X						X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type																									
Lymph nodes	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	–	–	+	+
Fibrosarcoma, metastatic						X																			
Thymus	–	+	–	+	–	–	–	–	+	+	–	–	–	–	+	–	+	–	–	+	–	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																					X				
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X								X															
Hepatocellular carcinoma							X	X		X		X	X		X			X			X			X	
Fibrosarcoma, metastatic						X																			
Hemangiosarcoma										X															
Hemangiosarcoma, unc prim or meta																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	N	N	+	+	+	+	N	+	+	+	N	+	+	+	+	N	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Squamous cell papilloma										X															
Squamous cell carcinoma							X																		
Fibrosarcoma											X														
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																								X	
Tubular-cell adenoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X						X				X								X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma								X																	
Parathyroid	–	–	+	–	+	–	+	+	–	–	+	+	–	+	–	+	+	–	–	+	–	+	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, unc prim or meta																						X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	+	+	+	+	–	–	–	+	+	–	+	–	–	+	+	+	+	+	+	+	–	–	–	+	–
Carcinoma, NOS														X											
Squamous cell carcinoma	X	X	X	X				X							X	X	X	X	X	X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X		X														X	X					X	
Zymbal gland	+	+	–	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																	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	N
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar carcin, metastatic		X																							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, metastatic														X											
Alveolar/bronchiolar carcin, metastatic					X																				
Fibrosarcoma, metastatic											X														X
Malignant lymphoma, NOS		X								X							X		X					
Malig. lymphoma, histiocytic type																									
Leukemia, NOS																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

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
WEEKS ON STUDY	104	104	102	104	104	104	100	093	104	089	104	083	104	094	043	104	064	104	102	062	091	091	094	104	078	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell carcinoma		X											X													2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma			X				X							X							X				X	9
Neurofibrosarcoma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic							X									X				X						7
Alveolar/bronchiolar adenoma			X																	X						8
Alveolar/bronchiolar carcinoma					X								X				X					X		X		12
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malig. lymphoma, histiocytic type											X															1
Lymph nodes	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	40
Fibrosarcoma, metastatic																										1
Thymus	–	+	–	–	–	+	–	+	+	–	+	–	+	–	+	+	–	+	+	–	+	–	–	+	+	21
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X	X		X																	X			6
Hepatocellular carcinoma	X	X					X			X		X				X	X		X							17
Fibrosarcoma, metastatic																										1
Hemangiosarcoma												X														2
Hemangiosarcoma, unc prim or meta																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	N	N	+	N	+	N	+	+	N	+	N	+	+	N	+	N	+	N	+	50*
Pancreas	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	–	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	44
Squamous cell papilloma																			X							2
Squamous cell carcinoma																										1
Fibrosarcoma																										1
Small intestine	+	+	+	+	+	+	–	–	+	–	+	–	+	+	–	+	+	+	+	+	+	–	+	+	+	40
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Tubular-cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma				X			X												X							7
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma																										1
Parathyroid	–	–	+	+	+	–	+	–	+	–	+	–	+	+	+	–	–	–	–	+	+	–	+	–	–	23
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	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, unc prim or meta																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	+	+	–	+	+	+	–	–	+	+	+	–	+	–	+	+	–	+	–	–	–	–	+	+	+	29
Carcinoma, NOS																										1
Squamous cell carcinoma	X	X		X					X				X						X					X		18
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS					X			X	X		X				X						X			X	X	13
Zymbal gland	–	+	+	–	–	–	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	40
Squamous cell carcinoma		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	N	50*
Hepatocellular carcinoma, metastatic												X														1
Alveolar/bronchiolar carcin, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS, metastatic																										1
Alveolar/bronchiolar carcin, metastatic																										1
Fibrosarcoma, metastatic																										2
Malignant lymphoma, NOS				X					X																	6
Malig. lymphoma, histiocytic type																					X					2
Leukemia, NOS														X												1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: 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	101	074	074	095	104	090	100	054	104	076	081	097	095	007	082	098	093	104	078	104	081	102	089	102	099
INTEGUMENTARY SYSTEM																									
Skin	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Squamous cell carcin, unc prim/meta																								X	
Sebaceous adenocarcinoma																		X							
Subcutaneous tissue	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X	X													
Fibrosarcoma																			X		X				
Hemangiosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic	X																								
Squamous cell carcinoma, metastatic													X			X			X						
Alveolar/bronchiolar adenoma		X		X							X	X											X		X
Alveolar/bronchiolar carcinoma		X		X	X		X						X											X	
Rhabdomyosarcoma, metastatic																									
Carcinosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic																									
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Hemangiosarcoma						X																			
Hemangiosarcoma, metastatic																									
Malignant lymphoma, NOS																									
Lymph nodes	+	–	–	+	+	+	+	–	+	–	–	+	+	+	+	–	+	+	–	+	+	+	+	–	+
Squamous cell carcinoma, metastatic																									
Carcinosarcoma, metastatic																									
Thymus	–	+	–	+	+	–	–	–	+	–	–	–	+	+	+	–	–	+	–	–	–	–	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																			X						
Rhabdomyosarcoma																									
Carcinosarcoma, metastatic																									
DIGESTIVE SYSTEM																									
Oral cavity	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 carcinoma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular carcinoma	X				X	X						X	X								X				
Hemangiosarcoma																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+
Squamous cell papilloma													X							X					
Squamous cell carcinoma													X												
Adenocarcinoma, NOS													X												
Small intestine	+	+	–	+	+	–	+	–	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carci, metastatic																									
Carcinosarcoma, unc prim or metastatic																									
Urinary bladder	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Cortical adenoma																				X					
Pheochromocytoma												X													
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Follicular-cell adenoma					X																				
Parathyroid	+	–	–	–	–	+	+	–	+	–	–	–	+	+	+	–	+	–	+	+	+	–	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic													X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	+	–	–	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+
Carcinoma, NOS	X				X																		X		
Squamous cell carcinoma							X		X	X	X	X	X			X	X	X				X		X	X
Carcinosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X											X								
Adenoma, NOS	X			X									X					X		X					
Zymbal gland	+	+	+	+	+	+	+	–	+	+	+	+	–	–	–	–	–	–	+	+	+	+	+	+	+
Squamous cell carcinoma				X	X	X	X		X	X		X								X					X
Carcinosarcoma																									
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	N
Hemangiosarcoma						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	N
Alveolar/bronchiolar carcin, metastatic							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																									
Alveolar/bronchiolar carcin, metastatic		X																							
Hemangiosarcoma, metastatic						X																			
Malignant lymphoma, NOS								X														X			X
Malig. lymphoma, undiffer type				X																					
Malig. lymphoma, histiocytic type			X														X			X					

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

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
WEEKS ON STUDY	099	104	096	003	095	088	087	095	104	095	090	081	100	102	024	097	096	104	101	097	093	097	102	102	088	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
Squamous cell carcinoma		X																								2
Squamous cell carc, unc prim/meta																										1
Sebaceous adenocarcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
Sarcoma, NOS																										2
Fibrosarcoma																			X							3
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Squamous cell carcinoma, metastatic			X			X	X						X								X					8
Alveolar/bronchiolar adenoma	X							X					X								X	X		X		12
Alveolar/bronchiolar carcinoma	X							X			X	X					X	X	X			X				14
Rhabdomyosarcoma, metastatic										X																1
Carcinosarcoma, metastatic																	X									1
Trachea	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic	X																									1
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic	X																									1
Malignant lymphoma, NOS														X												1
Lymph nodes	+	–	+	–	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Squamous cell carcinoma, metastatic													X													1
Carcinosarcoma, metastatic																						X				1
Thymus	+	–	–	+	–	–	–	+	+	–	–	–	–	–	+	+	+	–	–	+	–	–	+	–	–	19
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Rhabdomyosarcoma										X																1
Carcinosarcoma, metastatic																						X				1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma																			X							1
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	46
Liver	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma														X			X									3
Hepatocellular carcinoma		X										X														8
Hemangiosarcoma	X																									2
Bile duct	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	+	N	+	+	N	N	+	+	N	+	N	+	+	+	N	+	+	N	+	+	N	+	+	+	50*
Pancreas	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	–	+	+	–	–	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	39
Squamous cell papilloma																			X				X		X	5
Squamous cell carcinoma																										1
Adenocarcinoma, NOS																										1
Small intestine	–	+	–	+	+	–	–	–	+	–	–	+	+	+	+	–	+	+	–	+	+	–	+	+	+	34
Adenocarcinoma, NOS													X													1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcin, metastatic												X														1
Carcinosarcoma, unc prim or meta						X																				1
Urinary bladder	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	39
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma																										1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular-cell adenoma																										1
Parathyroid	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	+	17
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	50*
Testis	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	+	–	+	+	+	+	–	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	36
Carcinoma, NOS																										3
Squamous cell carcinoma	X		X		X	X			X		X		X	X		X		X	X	X	X	X		X	X	28
Carcinosarcoma																	X									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																	X									3
Adenoma, NOS		X										X		X					X				X	X	11
Zymbal gland	+	+	+	–	+	–	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	39
Squamous cell carcinoma	X	X	X		X			X	X					X							X	X	X	X	X	21
Carcinosarcoma																						X				1
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	N	50*
Hemangiosarcoma																										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	N	50*
Alveolar/bronchiolar carcin, metastatic							X																			2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastatic											X														X	2
Alveolar/bronchiolar carcin, metastatic																										1
Hemangiosarcoma, metastatic																										1
Malignant lymphoma, NOS		X						X	X							X	X		X				X			10
Malig. lymphoma, undiffer-type																										1
Malig. lymphoma, histiocytic type																										3

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: 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	104	104	104	104	103	103	099	104	099	030	003	058	104	103	104	104	104	104	029	038	104	104	095	103	090
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma														X											
Hemangiosarcoma									X																
Osteosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X			X							
Osteosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic														X											
Hemangiosarcoma, metastatic									X@																
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma															X							X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	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				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma				X				X							X						X				
Pheochromocytoma, malignant							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Follicular-cell adenoma																									
Parathyroid	–	+	–	–	–	+	–	–	–	+	+	–	–	–	–	–	–	–	–	+	–	–	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	N
Preputial/clitoral gland	+	–	+	+	–	–	–	+	–	–	–	–	+	+	+	+	+	+	–	–	+	+	–	–	–
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-cell tumor																X									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																							X		
SPECIAL SENSE ORGANS																									
Eye	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 melanoma																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS		X		X											X										
Zymbal gland	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Fibrosarcoma, metastatic														X											
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	N
Sarcoma, NOS																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																								X	
Malignant lymphoma, NOS	X	X				X						X	X	X		X		X					X		X
Malig. lymphoma, lymphocytic type																									

\+ : Tissue examined microscopically
– : Required tissue not examined microscopically
N : Necropsy, no autolysis, no microscopic examination
: : No tissue information submitted
X : Tumor incidence
@ : Multiple occurrence of morphology

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0262	0271	0282	0292	0301	0311	0322	0333	0344	0358	0364	0375	0383	0399	0400	0411	0422	0433	0444	0455	0466	0477	0488	0499	0501	TOTAL
WEEKS ON STUDY	1044	0804	1044	1044	1044	1044	0744	1044	1044	0847	1044	1044	0733	1044	1000	1044	1044	1044	1044	1044	0847	1044	0933	1044	1044	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma	X																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Hemangiosarcoma																										1
Osteosarcoma		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X				X						4
Osteosarcoma, metastatic		X																								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Lymph nodes	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	46
Fibrosarcoma, metastatic																										1
Hemangiosarcoma, metastatic																										1
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X						1
Hepatocellular carcinoma																							X			3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Stomach	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	43
Squamous cell papilloma							X																			1
Small intestine	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	40
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	40
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Adenoma, NOS					X		X	X		X	X				X	X	X		X					X		13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma														X												1
Pheochromocytoma																X			X							6
Pheochromocytoma, malignant							X																			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma	X					X								X												3
Parathyroid	–	–	–	–	–	–	–	–	–	+	+	+	–	+	–	+	–	+	–	–	–	+	–	–	+	15
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Islet-cell adenoma																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	*50
Preputial/clitoral gland	+	–	–	+	+	+	–	+	–	–	–	–	–	–	+	+	+	+	–	–	+	–	–	+		23
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																						X			X	2
Ovary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa-cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	+	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	*50
Malignant melanoma															X											1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X								X															5
Zymbal gland	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	43
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
Fibrosarcoma, metastatic																										1
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	N	*50
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS, metastatic																										1
Malignant lymphoma, NOS	X																			X		X				13
Malig. lymphoma, lymphocytic type								X			X															2

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: 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	104	104	102	101	081	104	104	080	104	102	104	104	104	088	089	103	087	104	104	032	001	001	001	001	001
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic				X																					
Hepatocellular carcinoma, metas					X																				
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS													X												
Lymph nodes	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+
Thymus	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X	X											X	X						
Hepatocellular carcinoma				X	X																				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
Squamous cell papilloma							X							X											
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	–	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+
Adenoma, NOS			X								X	X							X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	+	+	–	+	+
Follicular-cell adenoma																									
Parathyroid	–	+	–	–	+	–	+	–	+	–	+	+	–	+	–	–	–	–	+	–	–	–	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	N	+	+	N	+	+	N	N	N	N	N	+	+	+	+	N	N	+	N	N	+
Carcinoma, NOS				X												X									
Preputial/clitoral gland	+	+	–	–	–	+	+	–	+	–	+	–	+	–	–	–	–	+	+	–	–	–	–	–	–
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS				X																					
Malig. lymphoma, histiocytic type																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Luteoma																			X						
Granulosa-cell tumor		X																							
Mixed tumor, benign																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X																
Zymbal gland	+	+	+	+	–	–	–	+	+	+	+	+	–	+	–	+	+	+	–	–	–	+	–	–	–
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, undiffer-type														X											
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type			X																						
Malignant lymphoma, mixed type																		X							
Undifferentiated leukemia																				X					

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

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
WEEKS ON STUDY	081	104	070	104	094	104	104	104	104	104	104	104	093	104	099	104	104	104	083	097	078	104	104	094	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma	X				X																X			X		4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	47
Carcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metas																										1
Alveolar/bronchiolar adenoma																				X						2
Alveolar/bronchiolar carcinoma										X			X				X									3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																								X		2
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	43
Thymus	–	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X					X															X			X	8
Hepatocellular carcinoma										X			X													4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	45
Squamous cell papilloma			X																							3
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	39
Adenoma, NOS											X															5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular-cell adenoma																									X	1
Parathyroid	+	+	+	–	–	+	–	–	+	–	–	+	–	–	–	+	–	–	–	+	–	+	–	–	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	N	N	+	+	N	+	+	+	N	N	N	N	+	+	+	+	+	*50
Carcinoma, NOS																										2
Preputial/clitoral gland	–	+	–	–	–	+	+	–	–	+	+	+	–	+	–	+	–	+	–	–	–	+	+	–	+	21
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Malig. lymphoma, histiocytic type		X																								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Luteoma																	X									2
Granulosa-cell tumor																										1
Mixed tumor, benign										X																1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS								X		X			X				X					X				6
Zymbal gland	–	–	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	33
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS						X	X	X		X	X		X				X			X		X				15
Malig. lymphoma, undiffer-type																										1
Malig. lymphoma, lymphocytic type			X																X							2
Malig. lymphoma, histiocytic type															X											2
Malignant lymphoma, mixed type																										1
Undifferentiated leukemia																										1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: MID DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	087	104	095	092	104	104	104	091	104	104	102	104	096	104	099	104	090	091	097	104	071	104	104	102
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Squamous cell papilloma										X														
Keratoacanthoma							X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Sarcoma, NOS																								
Fibrosarcoma											X												X	X
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic			X																					
Islet-cell carcinoma, metastatic										X														
Alveolar/bronchiolar adenoma			X			X								X										
Alveolar/bronchiolar carcinoma						X		X											X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X										
Malignant lymphoma, NOS										X														
Malig. lymphoma, undiffer-type																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+
Thymus	+	+	–	+	–	+	+	–	+	–	–	–	+	–	+	–	–	+	+	+	+	+	+	–
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X							X													
Hepatocellular carcinoma						X				X		X		X					X			X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	N	+
Pancreas	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+
Stomach	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+
Squamous cell papilloma										X													X	
Small intestine	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+
Adenocarcinoma, NOS														X										
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular-cell adenocarcinoma																								X
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	–	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenoma, NOS							X		X						X							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X			X																			
Cortical adenoma																		X						
Pheochromocytoma						X																		
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Follicular-cell adenoma																								
Parathyroid	+	+	–	+	–	–	–	–	–	+	–	+	–	–	–	–	+	–	+	+	–	–	–	–
Pancreatic islets	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma										X														
REPRODUCTIVE SYSTEM																								
Mammary gland	N	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	N	+	+	+	N	+
Carcinoma, NOS			X			X	X																	
Carcinosarcoma																								
Preputial/clitoral gland	–	+	–	–	–	+	+	–	+	–	–	+	–	+	–	+	–	–	–	+	+	–	–	–
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X
Ovary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS							X																	
Luteoma										X									X					X
Granulosa-cell tumor							X																	
Tubular adenoma													X						X					
Mixed tumor, benign		X			X	X		X						X							X			
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X								X	X		X			X							
Zymbal gland	–	+	+	–	+	+	–	–	+	+	+	+	–	+	+	–	+		+	+	+	+	+	+
Squamous cell carcinoma																								
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
Osteosarcoma																								
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
Carcinoma, NOS, metastatic																								
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
Adenoca, NOS unc prim/meta																X								
Osteosarcoma, metastatic																								
Malignant lymphoma, NOS				X			X		X		X			X		X		X		X				
Malig. lymphoma, undiffer-type																								
Malig. lymphoma, lymphocytic type												X	X											
Malig. lymphoma, histiocytic type	X																							
Leukemia, NOS																								

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE
(Continued)

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
WEEKS ON STUDY	085	104	104	070	104	094	102	096	080	104	103	104	093	104	068	104	104	104	100	111	095	085	067	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Squamous cell papilloma																										1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Sarcoma, NOS																					X					1
Fibrosarcoma																										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic				X																						2
Islet-cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma	X													X												5
Alveolar/bronchiolar carcinoma		X			X																			X		6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Malig. lymphoma, undiffer-type											X															1
Lymph nodes	–	+	+	–	+	+	+	+	–	+	–	–	–	–	–	+	+	+	+	+	+	–	+	+	+	39
Thymus	+	+	+	–	+	–	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X										X	X						5
Hepatocellular carcinoma											X				X											8
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Squamous cell papilloma					X		X					X		X												6
Small intestine	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular-cell adenocarcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	45
Adenoma, NOS					X														X							6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																								X		3
Cortical adenoma																										1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular-cell adenoma			X																							1
Parathyroid	–	+	–	–	–	+	–	+	+	–	+	–	+	–	+	–	–	+	+	–	–	–	–	–	–	17
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet-cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	N	N	N	+	+	+	+	N	+	+	+	+	N	+	+	*50
Carcinoma, NOS				X			X																			5
Carcinosarcoma						X																				1
Preputial/clitoral gland	–	–	–	–	+	–	–	–	–	+	–	+	–	–	–	+	–	–	–	–	–	–	–	–	+	15
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS																	X									2
Luteoma																										3
Granulosa-cell tumor							X	X			X		X									X				6
Tubular adenoma																			X							3
Mixed tumor, benign	X	X											X					X							X	12
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS									X									X	X	X			X			10
Zymbal gland	–	+	+	+	+	+	–	+	–	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	37
Squamous cell carcinoma																		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													X													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	N	*50
Carcinoma, NOS, metastatic				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoca, NOS unc prim/meta																										1
Osteosarcoma, metastatic													X													1
Malignant lymphoma, NOS							X				X			X	X	X		X		X						16
Malig. lymphoma, undiffer-type																						X				1
Malig. lymphoma, lymphocytic type																										2
Malig. lymphoma, histiocytic type	X																						X			3
Leukemia, NOS						X		X																		2

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	104	091	072	103	104	088	104	048	093	090	064	083	104	076	104	083	094	084	097	087	084	099	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Fibrosarcoma						X																			
Hemangioma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic						X						X													
Carcinoma, NOS, unc prim or metasta																									
Squamous cell carcinoma, metastatic											X														
Hepatocellular carcinoma, metastatic				X													X								
Alveolar/bronchiolar adenoma	X				X																	X			
Alveolar/bronchiolar carcinoma					X										X										X
Granulosa-cell carcinoma, metastatic																									
Carcinosarcoma, metastatic																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	–	+	+	–	+	+	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma				X													X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+
Pancreas	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+
Squamous cell papilloma					X												X							X	
Small intestine	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	–	+	+	+	–	–	–	+	+	+	+	+	+	+	+	–	+	+	–	+
Adenoma, NOS					X		X																		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Cortical adenoma					X																				
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma							X																		
Parathyroid	+	+	+	+	–	+	–	–	+	–	–	–	–	–	+	+	–	+	–	+	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+
Carcinoma, NOS						X						X		X			X								X
Squamous cell carcinoma											X								X						
Carcinosarcoma															X							X			
Preputial/clitoral gland	+	–	–	–	+	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Leiomyoma													X												
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
Luteoma																									
Granulosa-cell tumor					X									X	X										
Granulosa-cell carcinoma																									
Tubular adenoma				X																					
Mixed tumor, benign	X								X				X											X	X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X											X				X						
Adenoma, NOS													X				X						X	X	
Zymbal gland	+	+	–	+	+	+	+	–	–	–	+	–	–	+	+	–	–	–	–	+	–	+	+	+	+
Squamous cell carcinoma															X										
Carcinosarcoma						X																			
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
Carcinoma, NOS, metastatic						X																			
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	N
Alveolar/bronchiolar ca, metastatic															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
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
Carcinoma, NOS, metastatic																								X	
Squamous cell ca, unc prim/meta																									
Malignant lymphoma, NOS		X	X				X		X	X						X		X			X				
Malig. lymphoma, undiffer-type																									
Malig. lymphoma, lymphocytic type								X																	
Malig. lymphoma, histiocytic type																					X				
Leukemia, NOS																				X					

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0262	0271	0284	0294	0308	0311	0323	0333	0341	0355	0366	0377	0381	0391	0404	0411	0422	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	1040	1000	1044	1044	0887	0003	0955	0666	0771	1044	0994	1041	0771	1044	1044	1044	0955	0777	1048	1093	1041	0997	0882	0995		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50	
Fibrosarcoma																									1	
Hemangioma																									1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, NOS, metastatic							X																		3	
Carcinoma, NOS, unc prim or metasta																				X					1	
Squamous cell carcinoma, metastatic																									1	
Hepatocellular carcinoma, metastatic																									1	
Alveolar/bronchiolar adenoma			X									X			X				X		X			X	2	
Alveolar/bronchiolar carcinoma																	X	X	X						9	
Granulosa-cell carcinoma, metastatic							X																		6	
Carcinosarcoma, metastatic																									1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1	
																									50	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Spleen	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Malignant lymphoma, mixed type										X															1	
Lymph nodes	+	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	45	
Thymus	+	−	+	+	−	+	−	+	+	−	−	+	+	+	+	+	−	+	+	−	−	+	−	−	32	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma				X											X					X				X	4	
Hepatocellular carcinoma				X													X								4	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	N	N	*50	
Pancreas	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+		43	
Esophagus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Stomach	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−		43	
Squamous cell papilloma	X														X										5	
Small intestine	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	−	41	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	−	+	+	+	+	−	−	40	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	−	+	+	−	+	−	−	+	+	+	+	+	+	−	+	+	+	+	−	−	35
Adenoma, NOS							X							X												4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Pheochromocytoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular-cell adenoma																										1
Parathyroid	−	+	−	+	+	+	+	−	−	−	+	+	−	−	−	+	−	+	+	+	+	−	+	−	+	24
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	+	N	N	+	N	N	+	N	N	N	*50
Carcinoma, NOS							X					X		X												8
Squamous cell carcinoma																										2
Carcinosarcoma	X									X																4
Preputial/clitoral gland	−	−	−	−	−	−	−	−	−	+	−	+	−	+	−	−	−	−	+	−	−	−	−	−	−	9
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS							X																			1
Leiomyoma																										1
Endometrial stromal polyp													X													1
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS														X												1
Luteoma	X														X											2
Granulosa-cell tumor			X									X	X										X			7
Granulosa-cell carcinoma							X																			1
Tubular adenoma												X			X											3
Mixed tumor, benign										X							X									7
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49	
SPECIAL SENSE ORGANS																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48	
Carcinoma, NOS							X																		4	
Adenoma, NOS																			X	X					6	
Zymbal gland	+	+	+	+	+	−	−	+	−	+	+	+	−	+	+	+	−	+	+	+	+	−	−	+	−	31
Squamous cell carcinoma	X									X																3
Carcinosarcoma																										1
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	*50	
Carcinoma, NOS, metastatic																									1	
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, metastatic																									1	
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	
Hemangiosarcoma																								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	
Carcinoma, NOS, metastatic																				X					1	
Squamous cell ca, unc prim/meta											X														2	
Malignant lymphoma, NOS	X						X					X		X					X			X			13	
Malig. lymphoma, undiffer-type																									1	
Malig. lymphoma, lymphocytic type		X							X									X							4	
Malig. lymphoma, histiocytic type																									1	
Leukemia, NOS					X																				2	

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)	
FIBROSIS, DIFFUSE	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL		1 (2%)		
HYPERPLASIA, BASAL CELL	1 (2%)			
HYPERKERATOSIS	1 (2%)	1 (2%)	3 (6%)	
ACANTHOSIS	1 (2%)	1 (2%)	2 (4%)	
PARAKERATOSIS			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)		
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			
RESPIRATORY SYSTEM				
*NASAL TURBINATE	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)		
#PERITRACHEAL TISSUE	(49)	(46)	(47)	(46)
INFLAMMATION, ACUTE FOCAL				2 (4%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
NECROSIS, FOCAL	1 (2%)			
#LUNG/BRONCHUS	(50)	(49)	(49)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
#BRONCHIAL MUCOSA	(50)	(49)	(49)	(50)
HYPERPLASIA, FOCAL	1 (2%)			
#BRONCHUS/MUSCULARIS	(50)	(49)	(49)	(50)
HYPERPLASIA, FOCAL	1 (2%)			
#LUNG	(50)	(49)	(49)	(50)
ASPIRATION, FOREIGN BODY		1 (2%)	2 (4%)	1 (2%)
CONGESTION, ACUTE	1 (2%)	1 (2%)	2 (4%)	1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	2 (4%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		1 (2%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
ABSCESS, NOS		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)	1 (2%)	1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC	2 (4%)	2 (4%)	2 (4%)	
INFLAMMATION GRANULOMATOUS FOCAL	3 (6%)	4 (8%)		
FOREIGN MATERIAL, NOS		2 (4%)		
ALVEOLAR MACROPHAGES			1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)			2 (4%)
#LUNG/ALVEOLI	(50)	(49)	(49)	(50)
CONGESTION, NOS				1 (2%)
EDEMA, NOS	1 (2%)			
HEMORRHAGE				2 (4%)
FOREIGN MATERIAL, NOS	1 (2%)		2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(50)	(48)	(47)	(48)
HYPOPLASIA, NOS	1 (2%)			
ATROPHY, DIFFUSE				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM				
#BONE MARROW (Continued)	(50)	(48)	(47)	(48)
MYELOFIBROSIS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC		1 (2%)	1 (2%)	
HYPERPLASIA, GRANULOCYTIC		4 (8%)	1 (2%)	6 (13%)
HYPERPLASIA, RETICULUM CELL	1 (2%)			
HYPOPLASIA, HEMATOPOIETIC				1 (2%)
#MARROW ERYTHROCYTES	(50)	(48)	(47)	(48)
ATROPHY, FOCAL				1 (2%)
#SPLEEN	(49)	(48)	(47)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)			
#SPLENIC FOLLICLES	(49)	(48)	(47)	(47)
LYMPHOID DEPLETION		19 (40%)	8 (17%)	23 (49%)
#SPLENIC RED PULP	(49)	(48)	(47)	(47)
CONGESTION, NOS			2 (4%)	
CONGESTION, ACUTE			1 (2%)	
FIBROSIS, MULTIFOCAL	1 (2%)			
PIGMENTATION, NOS		2 (4%)	4 (9%)	1 (2%)
HEMATOPOIESIS		4 (8%)	6 (13%)	6 (13%)
#LYMPH NODE	(42)	(37)	(34)	(37)
INFLAMMATION ACTIVE CHRONIC		1 (3%)		
#MANDIBULAR L. NODE	(42)	(37)	(34)	(37)
CYST, NOS	4 (10%)			
MULTIPLE CYSTS		1 (3%)		
CONGESTION, NOS			1 (3%)	
INFLAMMATION ACTIVE CHRONIC		1 (3%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION GRANULOMATOUS FOCAL				1 (3%)
HISTIOCYTOSIS	6 (14%)	14 (38%)	10 (29%)	7 (19%)
PLASMACYTOSIS			8 (24%)	1 (3%)
HYPERPLASIA, LYMPHOID	1 (2%)			
#THORACIC LYMPH NODE	(42)	(37)	(34)	(37)
PLASMACYTOSIS		1 (3%)		
#MESENTERIC L. NODE	(42)	(37)	(34)	(37)
INFLAMMATION GRANULOMATOUS FOCAL				1 (3%)
PLASMACYTOSIS	1 (2%)			
HYPERPLASIA, LYMPHOID	1 (2%)			
#RENAL LYMPH NODE	(42)	(37)	(34)	(37)
INFLAMMATION, CHRONIC FOCAL				1 (3%)
#BRACHIAL LYMPH NODE	(42)	(37)	(34)	(37)
HISTIOCYTOSIS				1 (3%)
#INGUINAL LYMPH NODE	(42)	(37)	(34)	(37)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
#THYMIC LYMPH NODE	(42)	(37)	(34)	(37)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			
ANGIECTASIS		1 (3%)		
HISTIOCYTOSIS		1 (3%)		
#LIVER	(50)	(48)	(49)	(49)
HEMATOPOIESIS		1 (2%)		1 (2%)
#PORTAL TRACT	(50)	(48)	(49)	(49)
HEMATOPOIESIS		1 (2%)		
#ADRENAL CORTEX	(50)	(49)	(48)	(49)
HEMATOPOIESIS				1 (2%)
#ZONA FASCICULATA	(50)	(49)	(48)	(49)
HEMATOPOIESIS				1 (2%)
#ZONA RETICULARIS	(50)	(49)	(48)	(49)
HEMATOPOIESIS		2 (4%)	3 (6%)	5 (10%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#THYMUS	(44)	(42)	(41)	(34)
EMBRYONAL DUCT CYST			2 (5%)	2 (6%)
CONGESTION, NOS		1 (2%)		
HEMORRHAGE		1 (2%)		
LYMPHOID DEPLETION		3 (7%)	6 (15%)	8 (24%)
#THYMIC CORTEX	(44)	(42)	(41)	(34)
LYMPHOID DEPLETION		1 (2%)	2 (5%)	2 (6%)
#THYMIC MEDULLA	(44)	(42)	(41)	(34)
HYPERPLASIA, EPITHELIAL		1 (2%)		
METAPLASIA, SQUAMOUS		1 (2%)		
CIRCULATORY SYSTEM				
#MANDIBULAR L. NODE	(42)	(37)	(34)	(37)
LYMPHANGIECTASIS	1 (2%)			1 (3%)
EMBOLUS, SEPTIC				1 (3%)
#MYOCARDIUM	(50)	(49)	(49)	(50)
MINERALIZATION		1 (2%)	1 (2%)	
INFLAMMATION, ACUTE NECROTIZING				1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
DEGENERATION, NOS	40 (80%)	43 (88%)	42 (86%)	34 (68%)
*CONJUNCTIVAL ARTERY	(50)	(50)	(50)	(50)
THROMBUS, CANALIZED	1 (2%)			
*HEPATIC VEIN	(50)	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
*CENTRAL VEINS/LIVER	(50)	(50)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)	2 (4%)
#LIVER	(50)	(48)	(49)	(49)
THROMBOSIS, NOS		2 (4%)		
#LIVER/CENTRILOBULAR	(50)	(48)	(49)	(49)
THROMBOSIS, NOS			1 (2%)	1 (2%)
#HEPATIC SINUSOID	(50)	(48)	(49)	(49)
CONGESTION, PASSIVE			1 (2%)	
DIGESTIVE SYSTEM				
*PALATE	(50)	(50)	(50)	(50)
HYPERKERATOSIS		2 (4%)		1 (2%)
ACANTHOSIS		2 (4%)		1 (2%)
*BUCCAL MUCOSA	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)	
*LIP	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
*TONGUE	(50)	(50)	(50)	(50)
ABSCESS, CHRONIC				1 (2%)
#SALIVARY GLAND	(49)	(49)	(47)	(49)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)		1 (2%)
FIBROSIS, MULTIFOCAL	1 (2%)			
BASOPHILIC CYTO CHANGE			1 (2%)	
ATROPHY, FOCAL	1 (2%)			2 (4%)
ATROPHY, DIFFUSE		1 (2%)		1 (2%)
METAPLASIA, SQUAMOUS		1 (2%)		
#LIVER	(50)	(48)	(49)	(49)
INFLAMMATION, ACUTE FOCAL		1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION GRANULOMATOUS FOCAL	7 (14%)	8 (17%)		1 (2%)
DEGENERATION, CYSTIC		1 (2%)		
NECROSIS, FOCAL	1 (2%)			

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER (Continued)	(50)	(48)	(49)	(49)
CYTOPLASMIC VACUOLIZATION		1 (2%)		
BASOPHILIC CYTO CHANGE	5 (10%)	6 (13%)	1 (2%)	1 (2%)
CLEAR-CELL CHANGE	2 (4%)	6 (13%)	11 (22%)	1 (2%)
ANGIECTASIS	1 (2%)			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(48)	(49)	(49)
NECROSIS, FOCAL	1 (2%)		1 (2%)	1 (2%)
#LIVER/PERIPORTAL	(50)	(48)	(49)	(49)
CYTOPLASMIC VACUOLIZATION		4 (8%)		1 (2%)
#LIVER/HEPATOCYTES	(50)	(48)	(49)	(49)
DEGENERATION, CYSTIC	1 (2%)		2 (4%)	1 (2%)
NECROSIS, FOCAL	1 (2%)		2 (4%)	1 (2%)
NECROSIS, CENTRAL				1 (2%)
CYTOPLASMIC VACUOLIZATION	6 (12%)	6 (13%)	6 (12%)	8 (16%)
#BILE DUCT	(50)	(48)	(49)	(49)
HYPERPLASIA, NOS	1 (2%)			1 (2%)
HYPERPLASIA, FOCAL	38 (76%)	40 (83%)	45 (92%)	38 (78%)
#PANCREAS	(49)	(44)	(47)	(49)
INFLAMMATION ACTIVE CHRONIC	1 (2%)			
#PANCREATIC ACINUS	(49)	(44)	(47)	(49)
CELL-SIZE, ALTERATION		1 (2%)		
ATROPHY, FOCAL	13 (27%)	11 (25%)	8 (17%)	7 (14%)
ATROPHY, DIFFUSE				1 (2%)
HYPERPLASIA, NOS	3 (6%)	2 (5%)		
HYPERPLASIA, FOCAL		1 (2%)	2 (4%)	
#ESOPHAGUS/MUSCULARIS	(49)	(49)	(48)	(49)
DEGENERATION, NOS	1 (2%)			
#PERIESOPHAGEAL TISSUE	(49)	(49)	(48)	(49)
HEMORRHAGE	1 (2%)			
INFLAMMATION, ACUTE FOCAL			2 (4%)	
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE FIBRINOUS	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#GASTRIC MUCOSA	(48)	(44)	(48)	(47)
MINERALIZATION		1 (2%)		
ULCER, ACUTE		1 (2%)		
#GASTRIC SUBMUCOSA	(48)	(44)	(48)	(47)
EDEMA, NOS			1 (2%)	
#CARDIAC STOMACH	(48)	(44)	(48)	(47)
ULCER, NOS	1 (2%)			
ULCER, FOCAL		1 (2%)		
ULCER, ACUTE		1 (2%)		2 (4%)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION ACTIVE CHRONIC				1 (2%)
ULCER, CHRONIC		1 (2%)		1 (2%)
EROSION				1 (2%)
HYPERKERATOSIS	2 (4%)	4 (9%)	3 (6%)	9 (19%)
ACANTHOSIS	2 (4%)	4 (9%)	3 (6%)	10 (21%)
#GASTRIC FUNDUS	(48)	(44)	(48)	(47)
ULCER, FOCAL	1 (2%)			
ULCER, ACUTE	1 (2%)		2 (4%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	2 (4%)			
INFLAMMATION, ACUTE NECROTIZING			1 (2%)	
NECROSIS, FOCAL	9 (19%)	10 (23%)	12 (25%)	5 (11%)
#JEJUNAL SUBMUCOSA	(44)	(42)	(45)	(44)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
#COLON	(47)	(42)	(46)	(46)
PARASITISM	1 (2%)	1 (2%)	3 (7%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(50)	(48)	(48)	(48)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
NEPHROPATHY	42 (84%)	43 (90%)	41 (85%)	45 (94%)
NEPHROSIS, NOS	1 (2%)		1 (2%)	
#KIDNEY/CORTEX	(50)	(48)	(48)	(48)
MULTIPLE CYSTS			1 (2%)	
NEPHROPATHY		1 (2%)		
METAMORPHOSIS FATTY		1 (2%)		
#KIDNEY/TUBULE	(50)	(48)	(48)	(48)
BACTERIAL SEPTICEMIA				1 (2%)
PIGMENTATION, NOS	1 (2%)			2 (4%)
#RENAL TUBULAR BASEMENT MEM	(50)	(48)	(48)	(48)
MINERALIZATION		1 (2%)		
#PAPILLARY DUCT/BELLI	(50)	(48)	(48)	(48)
MINERALIZATION			1 (2%)	
#KIDNEY/PELVIS	(50)	(48)	(48)	(48)
HYPERPLASIA, EPITHELIAL		1 (2%)		
#URINARY BLADDER	(48)	(43)	(47)	(44)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
#U. BLADDER/SUBMUCOSA	(48)	(43)	(47)	(44)
HEMORRHAGE			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(45)	(46)	(48)
EMBRYONAL DUCT CYST	1 (2%)	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)	1 (2%)
#ANTERIOR PITUITARY	(47)	(45)	(46)	(48)
EMBRYONAL DUCT CYST		4 (9%)		1 (2%)
CYST, NOS				1 (2%)
MULTIPLE CYSTS		1 (2%)		1 (2%)
CONGESTION, NOS		1 (2%)		
HEMORRHAGIC CYST		1 (2%)		
CYTOPLASMIC CHANGE, NOS		1 (2%)		
FOCAL CELLULAR CHANGE				1 (2%)
#PITUITARY CELL	(47)	(45)	(46)	(48)
CYTOPLASMIC VACUOLIZATION		1 (2%)		
FOCAL CELLULAR CHANGE		1 (2%)		
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	5 (11%)	8 (17%)	3 (6%)
HYPERPLASIA, DIFFUSE		1 (2%)		
#ADRENAL CORTEX	(50)	(49)	(48)	(49)
HEMORRHAGIC CYST		1 (2%)		
METAMORPHOSIS FATTY				2 (4%)
CYTOPLASMIC VACUOLIZATION		2 (4%)		2 (4%)
HYPERPLASIA, FOCAL		2 (4%)	1 (2%)	
#ZONA FASCICULATA	(50)	(49)	(48)	(49)
NECROSIS, FOCAL	1 (2%)			2 (4%)
METAMORPHOSIS FATTY		1 (2%)		
CYTOPLASMIC VACUOLIZATION		7 (14%)	8 (17%)	3 (6%)
FOCAL CELLULAR CHANGE	2 (4%)			1 (2%)
CLEAR-CELL CHANGE	1 (2%)			
HYPERPLASIA, FOCAL		13 (27%)		2 (4%)
#ADRENAL MEDULLA	(50)	(49)	(48)	(49)
FIBROSIS, MULTIFOCAL			1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	7 (14%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#THYROID	(49)	(47)	(46)	(47)
EMBRYONAL DUCT CYST			1 (2%)	
FOLLICULAR CYST, NOS	3 (6%)	5 (11%)		4 (9%)
HYPERPLASIA, CYSTIC				1 (2%)
HYPERPLASIA, C-CELL	7 (14%)	12 (26%)	7 (15%)	7 (15%)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	1 (2%)	1 (2%)
#THYROID CAPSULE	(49)	(47)	(46)	(47)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
#THYROID FOLLICLE	(49)	(47)	(46)	(47)
DILATATION, NOS	1 (2%)			
HYPERPLASIA, CYSTIC		2 (4%)		
#PARATHYROID	(33)	(38)	(37)	(44)
DILATATION, NOS			1 (3%)	
HYPERPLASIA, NOS		1 (3%)		
HYPERPLASIA, FOCAL				1 (2%)
#PANCREATIC ISLETS	(49)	(44)	(47)	(49)
HYPERPLASIA, FOCAL		2 (5%)	3 (6%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)	1 (2%)		
GALACTOCELE		3 (6%)		
MULTIPLE CYSTS				1 (2%)
HEMORRHAGIC CYST		1 (2%)		
HYPERPLASIA, CYSTIC	2 (4%)			2 (4%)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
*MAMMARY ACINUS	(50)	(50)	(50)	(50)
DILATATION, NOS			2 (4%)	1 (2%)
MULTIPLE CYSTS	1 (2%)			
HEMORRHAGIC CYST	1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		1 (2%)
HYPERPLASIA, CYSTIC	8 (16%)	8 (16%)	7 (14%)	10 (20%)
*PREPUCE	(50)	(50)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC	1 (2%)			
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CYST, NOS		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)		
#PROSTATE	(47)	(46)	(47)	(48)
HEMORRHAGE			1 (2%)	
INFLAMMATION ACTIVE CHRONIC		2 (4%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		2 (4%)	
INFLAMMATION, CHRONIC FOCAL	6 (13%)			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)			
HYPERPLASIA, FOCAL			1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			1 (2%)
HYPERPLASIA, FOCAL				1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)	
#TESTIS	(50)	(48)	(50)	(48)
EDEMA, INTERSTITIAL	1 (2%)			
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)		
DEGENERATION, NOS	1 (2%)			
HYPOSPERMATOGENESIS				1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	5 (10%)	4 (8%)	11 (22%)	19 (40%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#TESTIS/TUBULE	(50)	(48)	(50)	(48)
DEGENERATION, NOS	28 (56%)	29 (60%)	25 (50%)	18 (38%)
ATROPHY, FOCAL			1 (2%)	
ASPERMATOGENESIS	1 (2%)			
#TESTIS/INTERSTITIAL	(50)	(48)	(50)	(48)
HEMORRHAGE				1 (2%)
*EPIDIDYMIS	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(49)	(50)	(48)	(48)
INFLAMMATION, ACUTE FOCAL				2 (4%)
#CEREBRUM	(49)	(50)	(48)	(48)
HYDROCEPHALUS, NOS		1 (2%)		
ATROPHY, PRESSURE	1 (2%)	1 (2%)	1 (2%)	
#BRAIN	(49)	(50)	(48)	(48)
HEMORRHAGE				1 (2%)
#BRAIN/THALAMUS	(49)	(50)	(48)	(48)
ATROPHY, PRESSURE	1 (2%)			
#HYPOTHALAMUS	(49)	(50)	(48)	(48)
ATROPHY, PRESSURE	1 (2%)		1 (2%)	
#CEREBELLUM	(49)	(50)	(48)	(48)
HEMORRHAGE			1 (2%)	
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
SYNECHIA, ANTERIOR			1 (2%)	
NECROSIS, DIFFUSE			1 (2%)	
*EYE POSTERIOR CHAMBER	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
*EYE/CORNEA	(50)	(50)	(50)	(50)
ULCER, FOCAL	1 (2%)			
INFLAMMATION, ACUTE DIFFUSE			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)			
INFLAMMATION, CHRONIC FOCAL				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	5 (10%)	7 (14%)	1 (2%)	5 (10%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
CATARACT	4 (8%)	6 (12%)	2 (4%)	5 (10%)
#HARDERIAN GLAND	(49)	(49)	(49)	(50)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, CHRONIC	9 (18%)	8 (16%)	1 (2%)	1 (2%)
ATROPHY, NOS		3 (6%)		
HYPERPLASIA, NOS		4 (8%)		
HYPERPLASIA, EPITHELIAL				2 (4%)
HYPERPLASIA, FOCAL			1 (2%)	1 (2%)
#ZYMBAL GLAND	(32)	(46)	(42)	(42)
DILATATION/DUCTS	8 (25%)	35 (76%)	20 (48%)	28 (67%)
CYSTIC DUCTS	1 (3%)	7 (15%)	6 (14%)	
INFLAMMATION, SUPPURATIVE	1 (3%)	1 (2%)		
HYPERPLASIA, NOS		6 (13%)	1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)	3 (7%)
METAPLASIA, SQUAMOUS	1 (3%)			

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
OSTEOSCLEROSIS		5 (10%)		
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		1 (2%)	2 (4%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
INFLAMMATION, ACUTE NECROTIZING				1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, GRANULOMATOUS FOCAL	2 (4%)			
BACTERIAL SEPTICEMIA			1 (2%)	
NECROSIS, FOCAL			1 (2%)	
*PARIETAL PERITONEUM	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
*PLEURA	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)		
*PERICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			
*MESENTERY	(50)	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)	
INFLAMMATION, GRANULOMATOUS FOCAL	6 (12%)		5 (10%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)		
BACTERIAL SEPTICEMIA	1 (2%)			1 (2%)
HYPERPLASIA, FOCAL		2 (4%)		
ADIPOSE TISSUE				
HEMORRHAGE				1
INFLAMMATION GRANULOMATOUS FOCAL		2		
NECROSIS, FOCAL	1			
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
ULCER, CHRONIC		2 (4%)		
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	2 (4%)
HYPERKERATOSIS		2 (4%)		1 (2%)
ACANTHOSIS		3 (6%)		1 (2%)
METAPLASIA, NOS		1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
EOSINOPHILIC INFILTRATE				1 (2%)
INFLAMMATION, GRANULOMATOUS				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEAL MUCOSA	(50)	(48)	(49)	(48)
LACERATED WOUND	1 (2%)			
#PERITRACHEAL TISSUE	(50)	(48)	(49)	(48)
INFLAMMATION, GRANULOMATOUS FOCAL	1 (2%)			
#LUNG	(50)	(50)	(50)	(50)
ASPIRATION, FOREIGN BODY		2 (4%)		2 (4%)
CONGESTION, NOS	1 (2%)			1 (2%)
CONGESTION, ACUTE		1 (2%)	1 (2%)	1 (2%)
EDEMA, NOS				1 (2%)
INFLAMMATION, ACUTE FOCAL		3 (6%)		
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)		
PNEUMONIA INTERSTITIAL CHRONIC		3 (6%)		1 (2%)
INFLAMMATION, GRANULOMATOUS FOCAL	3 (6%)	1 (2%)		4 (8%)
PERIVASCULAR CUFFING	1 (2%)			
BACTERIAL SEPTICEMIA				1 (2%)
FOREIGN MATERIAL, NOS		1 (2%)	1 (2%)	
ALVEOLAR MACROPHAGES	2 (4%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	2 (4%)		1 (2%)
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
HISTIOCYTOSIS			1 (2%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(50)	(48)	(48)
METAMORPHOSIS FATTY	1 (2%)			
MYELOFIBROSIS	1 (2%)			1 (2%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)	2 (4%)	2 (4%)	4 (8%)
HYPERPLASIA, RETICULUM CELL	1 (2%)	1 (2%)		1 (2%)
HYPOPLASIA, HEMATOPOIETIC			1 (2%)	
APLASIA, HEMATOPOIETIC		2 (4%)	1 (2%)	
#SPLEEN	(50)	(50)	(49)	(49)
FIBROSIS, FOCAL				1 (2%)
LYMPHOID DEPLETION		1 (2%)	1 (2%)	2 (4%)
#SPLENIC FOLLICLES	(50)	(50)	(49)	(49)
LYMPHOID DEPLETION		10 (20%)	7 (14%)	8 (16%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#SPLENIC RED PULP	(50)	(50)	(49)	(49)
CONGESTION, ACUTE				1 (2%)
PIGMENTATION, NOS	1 (2%)	2 (4%)	4 (8%)	3 (6%)
HEMATOPOIESIS	2 (4%)		1 (2%)	8 (16%)
#MANDIBULAR L. NODE	(48)	(42)	(43)	(39)
HEMORRHAGE			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	2 (4%)			
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			1 (3%)
NECROSIS, FOCAL			2 (5%)	
PIGMENTATION, NOS				1 (3%)
LYMPHOID DEPLETION		1 (2%)	1 (2%)	
HISTIOCYTOSIS	19 (40%)	17 (40%)	22 (51%)	18 (46%)
PLASMACYTOSIS	1 (2%)			1 (3%)
#PANCREATIC L. NODE	(48)	(42)	(43)	(39)
HEMORRHAGE		1 (2%)		
HISTIOCYTOSIS		1 (2%)		
#MESENTERIC L. NODE	(48)	(42)	(43)	(39)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			1 (3%)
HISTIOCYTOSIS			1 (2%)	
#RENAL LYMPH NODE	(48)	(42)	(43)	(39)
HISTIOCYTOSIS		1 (2%)		
#INGUINAL LYMPH NODE	(48)	(42)	(43)	(39)
HISTIOCYTOSIS			1 (2%)	
#THYMIC LYMPH NODE	(48)	(42)	(43)	(39)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)		
PIGMENTATION, NOS	1 (2%)			1 (3%)
HISTIOCYTOSIS	1 (2%)	1 (2%)		1 (3%)
ERYTHROPHAGOCYTOSIS			1 (2%)	
#LIVER	(50)	(49)	(50)	(50)
HEMATOPOIESIS				2 (4%)
#PEYER'S PATCH	(50)	(48)	(47)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)	
#ZONA FASCICULATA	(50)	(50)	(47)	(49)
HEMATOPOIESIS			1 (2%)	
#THYMUS	(46)	(46)	(44)	(37)
EMBRYONAL DUCT CYST			1 (2%)	
LYMPHOID DEPLETION	2 (4%)		2 (5%)	2 (5%)
#THYMIC CORTEX	(46)	(46)	(44)	(37)
LYMPHOID DEPLETION		2 (4%)	2 (5%)	1 (3%)
#THYMIC MEDULLA	(46)	(46)	(44)	(37)
EMBRYONAL DUCT CYST				1 (3%)
METAPLASIA, SQUAMOUS				1 (3%)
CIRCULATORY SYSTEM				
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
PERIARTERITIS	1 (2%)			
#CEREBRUM	(50)	(50)	(50)	(50)
PERIARTERITIS		1 (2%)		
#LUNG	(50)	(50)	(50)	(50)
PERIVASCULITIS	3 (6%)	2 (4%)		
#MYOCARDIUM	(50)	(50)	(50)	(50)
MINERALIZATION			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			2 (4%)	
DEGENERATION, NOS	32 (64%)	31 (62%)	39 (78%)	30 (60%)
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
*PALATE	(50)	(50)	(50)	(50)
HYPERKERATOSIS	1 (2%)	3 (6%)	2 (4%)	3 (6%)
ACANTHOSIS	1 (2%)	3 (6%)	2 (4%)	3 (6%)
#SALIVARY GLAND	(50)	(50)	(48)	(50)
INFLAMMATION, ACUTE FOCAL		2 (4%)		
ATROPHY, FOCAL	1 (2%)	2 (4%)	1 (2%)	
#PAROTID DUCT	(50)	(50)	(48)	(50)
HYPERPLASIA, FOCAL		1 (2%)		
#LIVER	(50)	(49)	(50)	(50)
CONGESTION, ACUTE PASSIVE	1 (2%)			
INFLAMMATION, ACUTE FOCAL	2 (4%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)	2 (4%)
INFLAMMATION GRANULOMATOUS FOCAL	23 (46%)	13 (27%)	7 (14%)	6 (12%)
BASOPHILIC CYTO CHANGE	22 (44%)	37 (76%)	21 (42%)	15 (30%)
FOCAL CELLULAR CHANGE	1 (2%)			
CLEAR-CELL CHANGE	2 (4%)	3 (6%)	8 (16%)	1 (2%)
ANGIECTASIS			1 (2%)	1 (2%)
#HEPATIC CAPSULE	(50)	(49)	(50)	(50)
CONGESTION, NOS		1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(49)	(50)	(50)
NECROSIS, FOCAL		1 (2%)		1 (2%)
CYTOPLASMIC VACUOLIZATION			1 (2%)	
#LIVER/PERIPORTAL	(50)	(49)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	2 (4%)	2 (4%)
#LIVER/HEPATOCYTES	(50)	(49)	(50)	(50)
NECROSIS, NOS			1 (2%)	
NECROSIS, FOCAL	1 (2%)	1 (2%)		
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)	3 (6%)	
BASOPHILIC CYTO CHANGE			1 (2%)	
CLEAR-CELL CHANGE				1 (2%)
#BILE DUCT	(50)	(49)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL	21 (42%)	17 (35%)	20 (40%)	19 (38%)
#PANCREATIC ACINUS	(49)	(50)	(49)	(49)
ATROPHY, FOCAL	9 (18%)	8 (16%)	7 (14%)	12 (24%)
ATROPHY, DIFFUSE				1 (2%)
#GASTRIC PYLORIC GLAND	(50)	(50)	(48)	(49)
ULCER, ACUTE	1 (2%)			
#GASTRIC SUBMUCOSA	(50)	(50)	(48)	(49)
EDEMA, NOS				2 (4%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#CARDIAC STOMACH	(50)	(50)	(48)	(49)
HYPERKERATOSIS	2 (4%)			1 (2%)
ACANTHOSIS	2 (4%)			1 (2%)
#GASTRIC FUNDUS	(50)	(50)	(48)	(49)
DILATATION, NOS				1 (2%)
HEMORRHAGE			1 (2%)	
ULCER, ACUTE		1 (2%)	1 (2%)	
NECROSIS, FOCAL	16 (32%)	16 (32%)	8 (17%)	9 (18%)
#COLON	(48)	(49)	(45)	(48)
PARASITISM				2 (4%)
#CECUM	(48)	(49)	(45)	(48)
HEMORRHAGE	1 (2%)			
*RECTUM	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
*RECTAL SUBMUCOSA	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		

TABLE C2. ARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(49)
CONGESTION, ACUTE PASSIVE	1 (2%)			
NEPHROPATHY	16 (32%)	27 (54%)	34 (68%)	20 (41%)
BACTERIAL SEPTICEMIA				1 (2%)
NEPHROSIS, NOS	2 (4%)			
#KIDNEY/CORTEX	(50)	(50)	(50)	(49)
CYST, NOS				1 (2%)
NEPHROSIS, NOS	3 (6%)			
#KIDNEY/TUBULE	(50)	(50)	(50)	(49)
MINERALIZATION				1 (2%)
DILATATION, NOS		1 (2%)		
DEGENERATION, NOS				2 (4%)
PIGMENTATION, NOS		1 (2%)		
#KIDNEY/PELVIS	(50)	(50)	(50)	(49)
MINERALIZATION		1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)	
#URINARY BLADDER	(48)	(47)	(47)	(49)
CALCULUS,MICROSCOPIC EXAMINATION		1 (2%)		
INFLAMMATION ACTIVE CHRONIC			1 (2%)	
#U. BLADDER/MUCOSA	(48)	(47)	(47)	(49)
HYPERPLASIA, PAPILLARY			1 (2%)	
METAPLASIA, SQUAMOUS		1 (2%)		
#U. BLADDER/SUBMUCOSA	(48)	(47)	(47)	(49)
INFLAMMATION, CHRONIC FOCAL	2 (4%)			
ENDOCRINE SYSTEM				
#PITUITARY	(47)	(50)	(48)	(49)
HEMORRHAGE, CHRONIC			1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		
HYPERPLASIA, FOCAL			1 (2%)	
#ANTERIOR PITUITARY	(47)	(50)	(48)	(49)
EMBRYONAL DUCT CYST	7 (15%)	1 (2%)	8 (17%)	3 (6%)
CYST, NOS		2 (4%)		1 (2%)
MULTIPLE CYSTS		4 (8%)	2 (4%)	
CONGESTION, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
HEMORRHAGIC CYST		2 (4%)		1 (2%)
HEMORRHAGE, CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
FOCAL CELLULAR CHANGE				1 (2%)
#PITUITARY CELL	(47)	(50)	(48)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)	
HYPERPLASIA, FOCAL	5 (11%)	9 (18%)	4 (8%)	7 (14%)
#ADRENAL CORTEX	(50)	(50)	(47)	(49)
CONGESTION, NOS				1 (2%)
HEMORRHAGIC CYST		1 (2%)		
NECROSIS, FOCAL		1 (2%)		
LIPOIDOSIS				1 (2%)
CYTOPLASMIC VACUOLIZATION	2 (4%)	1 (2%)	1 (2%)	
CELL-SIZE, ALTERATION		1 (2%)		
#ZONA FASCICULATA	(50)	(50)	(47)	(49)
CYST, NOS				1 (2%)
CONGESTION, NOS			1 (2%)	
HEMORRHAGIC CYST				1 (2%)
DEGENERATION, NOS			1 (2%)	
DEGENERATION, CYSTIC		1 (2%)		
NECROSIS, FOCAL	1 (2%)		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	5 (10%)	4 (9%)	4 (8%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#ZONA FASCICULATA (Continued)	(50)	(50)	(47)	(49)
FOCAL CELLULAR CHANGE	1 (2%)			1 (2%)
CLEAR-CELL CHANGE	2 (4%)	2 (4%)		1 (2%)
CELL-SIZE, ALTERATION			1 (2%)	
HYPERPLASIA, NOS		2 (4%)		
HYPERPLASIA, FOCAL		15 (30%)		
#ZONA RETICULARIS	(50)	(50)	(47)	(49)
NECROSIS, FOCAL	3 (6%)			
#ADRENAL MEDULLA	(50)	(50)	(47)	(49)
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL		9 (18%)	2 (4%)	
#THYROID	(50)	(50)	(50)	(49)
ECTOPIA			1 (2%)	
EMBRYONAL DUCT CYST		1 (2%)		1 (2%)
THYROGLOSSAL DUCT CYST			1 (2%)	
CYSTIC FOLLICLES			1 (2%)	
FOLLICULAR CYST, NOS	2 (4%)	3 (6%)	2 (4%)	
HYPERPLASIA, PAPILLARY	1 (2%)			
HYPERPLASIA, C-CELL	13 (26%)	8 (16%)	6 (12%)	10 (20%)
HYPERPLASIA, FOLLICULAR-CELL			1 (2%)	
#THYROID FOLLICLE	(50)	(50)	(50)	(49)
MULTIPLE CYSTS	2 (4%)			
HYPERPLASIA, CYSTIC		1 (2%)	2 (4%)	1 (2%)
#PANCREATIC ISLETS	(49)	(50)	(49)	(49)
CELL-SIZE, ALTERATION			1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		2 (4%)		
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
GALACTOCELE	1 (2%)	4 (8%)	2 (4%)	
CYSTIC DUCTS	1 (2%)			
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)			
*MAMMARY ACINUS	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL	2 (4%)		1 (2%)	
HYPERPLASIA, CYSTIC	19 (38%)	17 (34%)	18 (36%)	13 (26%)
*CLITORAL GLAND	(50)	(50)	(50)	(50)
HYPERPLASIA, CYSTIC				1 (2%)
#UTERUS	(50)	(50)	(49)	(50)
DILATATION, NOS	9 (18%)	7 (14%)	9 (18%)	2 (4%)
#CERVIX UTERI	(50)	(50)	(49)	(50)
DIVERTICULUM		1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)			
HYPERPLASIA, FOCAL	2 (4%)	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, DIFFUSE		1 (2%)		
HYPERPLASIA, PAPILLARY	1 (2%)	1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	30 (60%)	31 (62%)	32 (65%)	34 (68%)
#ENDOMETRIAL STROMA	(50)	(50)	(49)	(50)
EDEMA, NOS	1 (2%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)		1 (2%)	
INFLAMMATION ACTIVE CHRONIC	1 (2%)		1 (2%)	
#OVARY/PAROVARIAN	(50)	(50)	(49)	(50)
ABSCESS, NOS				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#OVARY	(50)	(50)	(49)	(50)
FOLLICULAR CYST, NOS	1 (2%)	5 (10%)	4 (8%)	3 (6%)
PAROVARIAN CYST	3 (6%)	5 (10%)	7 (14%)	5 (10%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	2 (4%)	
ATROPHY, SENILE				1 (2%)
#OVARY/FOLLICLE	(50)	(50)	(49)	(50)
MULTIPLE CYSTS				1 (2%)
NERVOUS SYSTEM				
#LATERAL VENTRICLE	(50)	(50)	(50)	(50)
HYDROCEPHALUS, NOS		1 (2%)		
#CEREBRUM	(50)	(50)	(50)	(50)
ATROPHY, PRESSURE	1 (2%)	2 (4%)	4 (8%)	
#BRAIN	(50)	(50)	(50)	(50)
HYDROCEPHALUS, NOS	2 (4%)			
#HYPOTHALAMUS	(50)	(50)	(50)	(50)
ATROPHY, PRESSURE			1 (2%)	
#MEDULLA OBLONGATA	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		1 (2%)
SPECIAL SENSE ORGANS				
*EYE	(50)	(50)	(50)	(50)
MICROPHTHALMIA		1 (2%)		
*EYE ANTERIOR CHAMBER	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
*EYE/CORNEA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
*EYE/RETINA	(50)	(50)	(50)	(50)
DEGENERATION, NOS	4 (8%)	6 (12%)	5 (10%)	7 (14%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)
CATARACT	3 (6%)	5 (10%)	4 (8%)	4 (8%)
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
INFLAMMATION, NOS		1 (2%)		
INFLAMMATION, CHRONIC	33 (67%)	26 (53%)	17 (34%)	7 (15%)
PORPHYRIN		2 (4%)		
ATROPHY, NOS			1 (2%)	
ATROPHY, FOCAL		1 (2%)	1 (2%)	
HYPERPLASIA, NOS		1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			1 (2%)
METAPLASIA, SQUAMOUS				1 (2%)
#ZYMBAL GLAND	(45)	(40)	(44)	(46)
DILATATION/DUCTS	15 (33%)	22 (55%)	28 (64%)	23 (50%)
CYSTIC DUCTS	1 (2%)	2 (5%)	8 (18%)	3 (7%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)	
HYPERPLASIA, FOCAL			6 (14%)	1 (2%)
METAPLASIA, SQUAMOUS				2 (4%)
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
OSTEOSCLEROSIS	8 (16%)	8 (16%)	7 (14%)	3 (6%)
FIBROUS DYSPLASIA	1 (2%)			

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
GRANULOMA, FOREIGN BODY			1 (2%)	
*PLEURA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
*EPICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
*MESENTERY	(50)	(50)	(50)	(50)
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)	
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
INFLAMMATION GRANULOMATOUS FOCAL				1
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED				1

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
ULCER, NOS		2 (4%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		1 (2%)
ULCER, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL			2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL		2 (4%)		
HYPERKERATOSIS		1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
MULTIPLE CYSTS	1 (2%)			
EDEMA, NOS		1 (2%)		
INFLAMMATION, MULTIFOCAL	1 (2%)			
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
ABSCESS, NOS			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		4 (8%)		
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)	2 (4%)
INFLAMMATION GRANULOMATOUS FOCAL		3 (6%)		
INFECTION, FUNGAL		1 (2%)		
NECROSIS, FOCAL		1 (2%)		
METAPLASIA, OSSEOUS		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(50)	(50)	(50)	(50)
MINERALIZATION	1 (2%)		1 (2%)	
CONGESTION, ACUTE	1 (2%)			
HEMORRHAGE	2 (4%)		3 (6%)	6 (12%)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)			
INFLAMMATION, INTERSTITIAL		1 (2%)	1 (2%)	
PNEUMONIA, ASPIRATION		2 (4%)	2 (4%)	2 (4%)
INFLAMMATION, ACUTE FOCAL	1 (2%)			2 (4%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC		1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)	
INFLAMMATION GRANULOMATOUS FOCAL				1 (2%)
PERIVASCULAR CUFFING				1 (2%)
ALVEOLAR MACROPHAGES	3 (6%)		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	3 (6%)	7 (14%)	10 (20%)
HISTIOCYTOSIS	2 (4%)	2 (4%)		3 (6%)
#LUNG/ALVEOLI	(50)	(50)	(50)	(50)
ASPIRATION, FOREIGN BODY		1 (2%)		
INFLAMMATION, INTERSTITIAL		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
*BLOOD	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS			1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#BONE MARROW	(49)	(50)	(50)	(49)
HEMORRHAGE		1 (2%)		
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)	
NECROSIS, FOCAL		1 (2%)		
HEMOSIDEROSIS				1 (2%)
HYPERPLASIA, DIFFUSE		1 (2%)	1 (2%)	1 (2%)
ANGIECTASIS			1 (2%)	
MYELOFIBROSIS				1 (2%)
HYPERPLASIA, HEMATOPOIETIC		11 (22%)	10 (20%)	25 (51%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)		2 (4%)	2 (4%)
HEMATOPOIESIS			2 (4%)	
#SPLEEN	(50)	(50)	(49)	(47)
ECTOPIA				1 (2%)
HEMORRHAGE		1 (2%)	2 (4%)	
NECROSIS, FOCAL			1 (2%)	1 (2%)
AMYLOIDOSIS		1 (2%)		
LYMPHOID DEPLETION	4 (8%)	2 (4%)	3 (6%)	11 (23%)
HYPERPLASIA, LYMPHOID	2 (4%)	3 (6%)	1 (2%)	1 (2%)
HEMATOPOIESIS	3 (6%)	8 (16%)	17 (35%)	23 (49%)
#SPLENIC CAPSULE	(50)	(50)	(49)	(47)
FIBROSIS, FOCAL		1 (2%)		
#SPLENIC FOLLICLES	(50)	(50)	(49)	(47)
NECROSIS, FOCAL		1 (2%)		
#SPLENIC RED PULP	(50)	(50)	(49)	(47)
HEMATOPOIESIS	2 (4%)	1 (2%)	2 (4%)	1 (2%)
#LYMPH NODE	(42)	(41)	(40)	(37)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
HEMOSIDEROSIS			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	3 (8%)
#MANDIBULAR L. NODE	(42)	(41)	(40)	(37)
HEMORRHAGE	1 (2%)			1 (3%)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
PIGMENTATION, NOS	1 (2%)			
HEMOSIDEROSIS	2 (5%)			
LYMPHOID DEPLETION			1 (3%)	
HISTIOCYTOSIS	1 (2%)			
PLASMACYTOSIS		2 (5%)	2 (5%)	3 (8%)
ERYTHROPHAGOCYTOSIS			1 (3%)	
HYPERPLASIA, PLASMA CELL			1 (3%)	
HYPERPLASIA, RETICULUM CELL			1 (3%)	1 (3%)
HYPERPLASIA, LYMPHOID	11 (26%)	1 (2%)	4 (10%)	
#CERVICAL LYMPH NODE	(43)	(41)	(40)	(37)
PLASMACYTOSIS			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#BRONCHIAL LYMPH NODE	(43)	(41)	(40)	(37)
HEMORRHAGE	1 (2%)			
#MEDIASTINAL L. NODE	(43)	(41)	(40)	(37)
LYMPHOID DEPLETION	1 (2%)			
#PANCREATIC L. NODE	(43)	(41)	(40)	(37)
HEMORRHAGE		1 (2%)		1 (3%)
INFLAMMATION, ACUTE/CHRONIC				1 (3%)
ANGIECTASIS			1 (3%)	
HYPERPLASIA, LYMPHOID		1 (2%)	1 (3%)	
HEMATOPOIESIS			1 (3%)	1 (3%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#MESENTERIC L. NODE	(43)	(41)	(40)	(37)
DILATATION, NOS			3 (8%)	
EDEMA, NOS	1 (2%)			
HEMORRHAGE	1 (2%)		2 (5%)	
INFLAMMATION, ACUTE DIFFUSE			1 (3%)	
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
LYMPHOID DEPLETION	1 (2%)	1 (2%)		1 (3%)
ANGIECTASIS		3 (7%)	1 (3%)	3 (8%)
LEUKEMOID REACTION		1 (2%)		
PLASMACYTOSIS				1 (3%)
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (3%)	
HEMATOPOIESIS		3 (7%)	4 (10%)	2 (5%)
#RENAL LYMPH NODE	(43)	(41)	(40)	(37)
INFLAMMATION, ACUTE/CHRONIC			1 (3%)	
PLASMACYTOSIS	1 (2%)			
HYPERPLASIA, LYMPHOID				1 (3%)
#AXILLARY LYMPH NODE	(43)	(41)	(40)	(37)
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#THYMIC LYMPH NODE	(43)	(41)	(40)	(37)
HEMORRHAGE				1 (3%)
INFLAMMATION GRANULOMATOUS FOCAL			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#LIVER	(50)	(50)	(50)	(48)
HEMATOPOIESIS	1 (2%)	1 (2%)	3 (6%)	5 (10%)
#KIDNEY	(50)	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID				1 (2%)
#PITUITARY	(46)	(43)	(42)	(39)
HYPERPLASIA, EOSINOPHILIC			1 (2%)	
#THYMUS	(34)	(27)	(21)	(19)
MINERALIZATION	1 (3%)			
LYMPHOID DEPLETION	2 (6%)			
HYPERPLASIA, EPITHELIAL		1 (4%)		
HYPERPLASIA, RETICULUM CELL			1 (5%)	
HYPERPLASIA, LYMPHOID		2 (7%)		
#THYMIC CORTEX	(34)	(27)	(21)	(19)
LYMPHOID DEPLETION	3 (9%)	1 (4%)	1 (5%)	1 (5%)
#THYMIC MEDULLA	(34)	(27)	(21)	(19)
INFLAMMATION, ACUTE DIFFUSE		1 (4%)		
#THYMIC LYMPHOCYTES	(34)	(27)	(21)	(19)
NECROSIS, NOS	1 (3%)			
NECROSIS, DIFFUSE		1 (4%)		1 (5%)
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)		1 (2%)
#BONE MARROW	(49)	(50)	(50)	(49)
THROMBUS, ORGANIZED			1 (2%)	
#LUNG	(50)	(50)	(50)	(50)
PERIVASCULITIS		1 (2%)		
#HEART	(49)	(50)	(50)	(50)
MINERALIZATION	2 (4%)	1 (2%)		1 (2%)
THROMBOSIS, NOS			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)	
#AURICULAR APPENDAGE	(49)	(50)	(50)	(50)
HYPERTROPHY, NOS				1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#RIGHT VENTRICLE	(49)	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)	
DEGENERATION, NOS				1 (2%)
#LEFT VENTRICLE	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
DEGENERATION, NOS				1 (2%)
#MYOCARDIUM	(49)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
INFLAMMATION, MULTIFOCAL				1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
DEGENERATION, NOS	1 (2%)	2 (4%)	3 (6%)	1 (2%)
#ENDOCARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
#TRICUSPID VALVE	(49)	(50)	(50)	(50)
PIGMENTATION, NOS				1 (2%)
*ARTERY	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
*AORTA	(50)	(50)	(50)	(50)
MINERALIZATION			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
EMBOLUS, SEPTIC			1 (2%)	
*ADRENAL ARTERY	(50)	(50)	(50)	(50)
PIGMENTATION, NOS	1 (2%)			
#PERIPROSTATIC TISSUE	(50)	(50)	(50)	(50)
PERIARTERITIS	1 (2%)			
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(49)	(50)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)			
INFLAMMATION, CHRONIC FOCAL	13 (26%)	11 (22%)	11 (22%)	2 (4%)
AMYLOIDOSIS				1 (2%)
ATROPHY, FOCAL		1 (2%)		
#PAROTID GLAND	(50)	(49)	(50)	(46)
ATROPHY, DIFFUSE			1 (2%)	
#LIVER	(50)	(50)	(50)	(48)
MINERALIZATION				1 (2%)
CONGESTION, CHRONIC PASSIVE			1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)	1 (2%)
NECROSIS, FOCAL	1 (2%)		1 (2%)	3 (6%)
NECROSIS, DIFFUSE	1 (2%)			
NECROSIS, COAGULATIVE	3 (6%)	1 (2%)	4 (8%)	1 (2%)
NUCLEAR-SIZE ALTERATION				1 (2%)
BASOPHILIC CYTO CHANGE	2 (4%)			
FOCAL CELLULAR CHANGE	1 (2%)			
CLEAR-CELL CHANGE	1 (2%)			
CYTOPLASMIC MATRIX, ALTERATION		1 (2%)		
CELL-SIZE, ALTERATION	1 (2%)	6 (12%)	5 (10%)	1 (2%)
N-C RATIO, ALTERATION	1 (2%)			
ANGIECTASIS				1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)	(48)
NECROSIS, FOCAL		1 (2%)		
NECROSIS, DIFFUSE	1 (2%)			
#LIVER/HEPATOCYTES	(50)	(50)	(50)	(48)
NECROSIS, FOCAL	1 (2%)			
NUCLEAR ENLARGEMENT	1 (2%)			
FOCAL CELLULAR CHANGE			1 (2%)	
CELL-SIZE, ALTERATION		1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
*GALLBLADDER	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)	
HYPERPLASIA, EPITHELIAL				1 (2%)
#BILE DUCT	(50)	(50)	(50)	(48)
HYPERPLASIA, FOCAL	1 (2%)			
#PANCREAS	(49)	(47)	(48)	(46)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	2 (4%)			1 (2%)
NECROSIS, COAGULATIVE			1 (2%)	
AMYLOIDOSIS				1 (2%)
#PANCREATIC ACINUS	(49)	(47)	(48)	(46)
ATROPHY, FOCAL	1 (2%)	1 (2%)	3 (6%)	4 (9%)
ATROPHY, DIFFUSE		1 (2%)	1 (2%)	1 (2%)
#PERIPANCREATIC TISSUE	(49)	(47)	(48)	(46)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
NECROSIS, FOCAL			1 (2%)	
#ESOPHAGUS	(50)	(50)	(50)	(48)
PENETRATING WOUND		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
NECROSIS, FOCAL				1 (2%)
#PERIESOPHAGEAL TISSUE	(50)	(50)	(50)	(48)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
#STOMACH	(46)	(44)	(44)	(39)
HEMORRHAGE	1 (2%)			
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
EROSION	1 (2%)			
HYPERPLASIA, EPITHELIAL		1 (2%)		
#GASTRIC MUCOSA	(46)	(44)	(44)	(39)
NECROSIS, FOCAL		1 (2%)		
HYPERKERATOSIS				1 (3%)
ACANTHOSIS				1 (3%)
#GASTRIC FUNDAL GLAND	(46)	(44)	(44)	(39)
DILATATION, NOS	1 (2%)			
#GLANDULAR STOMACH	(46)	(44)	(44)	(39)
DILATATION, NOS				1 (3%)
#CARDIAC STOMACH	(46)	(44)	(44)	(39)
CYST, NOS		1 (2%)	1 (2%)	
ULCER, NOS	1 (2%)			
ULCER, ACUTE		1 (2%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (4%)			
CELL-SIZE, ALTERATION				1 (3%)
HYPERPLASIA, EPITHELIAL	1 (2%)	10 (23%)	2 (5%)	
HYPERPLASIA, FOCAL			2 (5%)	
HYPERKERATOSIS	1 (2%)	7 (16%)	4 (9%)	
#GASTRIC FUNDUS	(46)	(44)	(44)	(39)
MINERALIZATION			1 (2%)	
ULCER, NOS			1 (2%)	1 (3%)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
EROSION			1 (2%)	
NECROSIS, FOCAL				1 (3%)
METAPLASIA, SQUAMOUS			1 (2%)	
#DUODENUM	(46)	(37)	(40)	(34)
PARASITISM	1 (2%)			
#JEJUNUM	(46)	(37)	(40)	(34)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
PARASITISM	1 (2%)			
HYPERPLASIA, FOCAL		1 (3%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#JEJUNAL SUBMUCOSA	(46)	(37)	(40)	(34)
INFLAMMATION, CHRONIC FOCAL				1 (3%)
#COLON	(50)	(50)	(49)	(48)
PARASITISM		3 (6%)	4 (8%)	6 (13%)
#CECUM	(50)	(50)	(49)	(48)
PARASITISM	1 (2%)			3 (6%)
*RECTUM	(50)	(50)	(50)	(50)
NECROSIS, FOCAL			1 (2%)	
HYPERPLASIA, DIFFUSE			1 (2%)	
URINARY SYSTEM				
*U. BLADDER/CAVITY	(46)	(44)	(43)	(41)
RETENTION OF CONTENT				1 (2%)
#KIDNEY	(50)	(50)	(50)	(49)
EMBRYONAL REST	1 (2%)	1 (2%)		
MINERALIZATION		1 (2%)	2 (4%)	
HYDRONEPHROSIS				3 (6%)
CYST, NOS	1 (2%)		1 (2%)	
PYELONEPHRITIS, FOCAL			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
PYELONEPHRITIS, ACUTE		1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)			
ABSCESS, NOS			1 (2%)	
PYELONEPHRITIS, ACUTE/CHRONIC			1 (2%)	
GLOMERULONEPHRITIS, CHRONIC	1 (2%)	1 (2%)	2 (4%)	
PYELONEPHRITIS, CHRONIC			1 (2%)	
NEPHROPATHY	28 (56%)	20 (40%)	24 (48%)	15 (31%)
GLOMERULOSCLEROSIS, NOS			2 (4%)	
INFARCT, FOCAL		1 (2%)	1 (2%)	2 (4%)
INFARCT, ACUTE			1 (2%)	1 (2%)
CLEAR-CELL CHANGE	1 (2%)			
HYPERPLASIA, TUBULAR CELL				1 (2%)
#PERIRENAL TISSUE	(50)	(50)	(50)	(49)
INFLAMMATION, ACUTE FOCAL				1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)	(49)
MINERALIZATION	1 (2%)			
DILATATION, NOS	2 (4%)			
NECROSIS, FOCAL	2 (4%)			
PIGMENTATION, NOS			2 (4%)	
ATROPHY, FOCAL			1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)	(49)
MINERALIZATION			1 (2%)	
HEMORRHAGE				1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
NECROSIS, COAGULATIVE			1 (2%)	
#URINARY BLADDER	(46)	(44)	(43)	(41)
CALCULUS,GROSS OBSERVATION ONLY			1 (2%)	
DILATATION, NOS				1 (2%)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	4 (9%)	2 (5%)	7 (16%)	4 (10%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
HYPERPLASIA, DIFFUSE			1 (2%)	
#U. BLADDER/MUCOSA	(46)	(44)	(43)	(41)
MINERALIZATION	1 (2%)			
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
#U. BLADDER/SUBMUCOSA	(46)	(44)	(43)	(41)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
*URETHRA	(50)	(50)	(50)	(50)
RETENTION OF CONTENT				1 (2%)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
*URETHRAL MUCOSA	(50)	(50)	(50)	(50)
EROSION		1 (2%)		
*PROSTATIC URETHRA	(50)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)			
RETENTION OF CONTENT	2 (4%)	1 (2%)		1 (2%)
HEMORRHAGE				1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(43)	(42)	(39)
CYST, NOS		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		
#ADRENAL	(48)	(50)	(49)	(47)
FOCAL CELLULAR CHANGE			1 (2%)	
#ADRENAL/CAPSULE	(48)	(50)	(49)	(47)
FIBROSIS, MULTIFOCAL				1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	32 (64%)	14 (29%)	4 (9%)
#ADRENAL CORTEX	(48)	(50)	(49)	(47)
DEGENERATION, NOS			1 (2%)	1 (2%)
DEGENERATION, HYALINE	1 (2%)			
LIPOIDOSIS				1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)	11 (22%)	8 (16%)	6 (13%)
CYTOPLASMIC MATRIX, ALTERATION	3 (6%)		1 (2%)	
CELL-SIZE, ALTERATION			1 (2%)	
HYPERTROPHY, FOCAL				2 (4%)
HYPERPLASIA, FOCAL	1 (2%)			1 (2%)
#ZONA FASCICULATA	(48)	(50)	(49)	(47)
LIPOIDOSIS			1 (2%)	
#ADRENAL MEDULLA	(48)	(50)	(49)	(47)
FIBROSIS, FOCAL			1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	5 (10%)	9 (18%)	2 (4%)
#PERIADRENAL TISSUE	(48)	(50)	(49)	(47)
HEMORRHAGE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
#THYROID	(48)	(49)	(49)	(45)
CYST, NOS			1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)		1 (2%)
HYPERPLASIA, FOCAL		3 (6%)		
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	2 (4%)	1 (2%)	3 (7%)
#PANCREATIC ISLETS	(49)	(47)	(48)	(46)
HYPERPLASIA, FOCAL		6 (13%)	2 (4%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	1 (2%)			
*MAMMARY ACINUS	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL				1 (2%)
*EPIDIDYMAL LUMEN	(50)	(50)	(50)	(50)
DILATATION, NOS		2 (4%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
*PENIS	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
*PREPUCE	(50)	(50)	(50)	(50)
ULCER, NOS		1 (2%)		
ULCER, ACUTE			1 (2%)	
INFLAMMATION, ACUTE NECROTIZING	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
#PREPUTIAL GLAND	(22)	(28)	(29)	(36)
DILATATION, NOS	1 (5%)			
DILATATION/DUCTS	2 (9%)		1 (3%)	
CYST, NOS		1 (4%)		
ULCER, NOS	1 (5%)			
INFLAMMATION, ACUTE	1 (5%)	1 (4%)		
INFLAMMATION, ACUTE FOCAL	3 (14%)		1 (3%)	1 (3%)
INFLAMMATION, ACUTE DIFFUSE				1 (3%)
ABSCESS, NOS		1 (4%)		
INFLAMMATION, ACUTE/CHRONIC	4 (18%)	5 (18%)	6 (21%)	1 (3%)
INFLAMMATION, CHRONIC FOCAL	5 (23%)	10 (36%)	2 (7%)	
HYPERPLASIA, EPITHELIAL		17 (61%)	9 (31%)	1 (3%)
HYPERPLASIA, FOCAL		1 (4%)		
HYPERPLASIA, DIFFUSE	1 (5%)			
HYPERKERATOSIS		2 (7%)	2 (7%)	1 (3%)
METAPLASIA, SQUAMOUS		2 (7%)		
#PROSTATE	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL	8 (16%)	1 (2%)	2 (4%)	3 (6%)
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
DILATATION, NOS	2 (4%)	5 (10%)	7 (14%)	3 (6%)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
ATROPHY, DIFFUSE			1 (2%)	
HYPERPLASIA, DIFFUSE	1 (2%)			
#TESTIS	(50)	(50)	(50)	(48)
MINERALIZATION		1 (2%)		1 (2%)
SPERMATOCELE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
ATROPHY, DIFFUSE			1 (2%)	1 (2%)
#TESTIS/TUBULE	(50)	(50)	(50)	(48)
MINERALIZATION			1 (2%)	1 (2%)
DEGENERATION, NOS				1 (2%)
#SPERMATOGENIC EPITHE	(50)	(50)	(50)	(48)
MINERALIZATION		1 (2%)	1 (2%)	
DEGENERATION, NOS		2 (4%)		
SYNCYTIAL ALTERATION		1 (2%)		
HYPOPLASIA, NOS		1 (2%)		
ATROPHY, FOCAL		1 (2%)		
ATROPHY, DIFFUSE			2 (4%)	2 (4%)
*EPIDIDYMIS	(50)	(50)	(50)	(50)
MINERALIZATION		1 (2%)		
HEMORRHAGE			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (4%)	2 (4%)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			
GRANULOMA, SPERMATIC			2 (4%)	
HYPERPLASIA, EPITHELIAL		1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
NERVOUS SYSTEM				
*PERIPHERAL NERVE	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
#CEREBRUM	(50)	(50)	(50)	(50)
MALACIA			1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
MINERALIZATION	1 (2%)			
HEMORRHAGE	1 (2%)		1 (2%)	2 (4%)
#BRAIN/THALAMUS	(50)	(50)	(50)	(50)
MINERALIZATION	12 (24%)	24 (48%)	18 (36%)	16 (32%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
#MEDULLA OBLONGATA	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(50)	(50)	(50)	(50)
ULCER, NOS			2 (4%)	
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)
RUPTURE			1 (2%)	
CATARACT	1 (2%)		1 (2%)	
*EYE/CONJUNCTIVA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
*EYE/LACRIMAL GLAND	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
*NASOLACRIMAL DUCT	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL				1 (2%)
#HARDERIAN GLAND	(50)	(48)	(49)	(49)
MINERALIZATION				1 (2%)
DISTENTION	1 (2%)			
RETENTION OF CONTENT		1 (2%)		
INFLAMMATION, MULTIFOCAL		1 (2%)		
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL	16 (32%)	8 (17%)	11 (22%)	7 (14%)
INFLAMMATION GRANULOMATOUS FOCAL			1 (2%)	
FIBROSIS, MULTIFOCAL				1 (2%)
DEGENERATION, NOS	1 (2%)			
NECROSIS, FOCAL				1 (2%)
ATROPHY, FOCAL		2 (4%)	1 (2%)	1 (2%)
ATROPHY, DIFFUSE		1 (2%)		
HYPERPLASIA, FOCAL		5 (10%)	11 (22%)	7 (14%)
METAPLASIA, NOS			1 (2%)	
*EAR CANAL	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
#ZYMBAL GLAND	(43)	(34)	(40)	(39)
DILATATION, NOS				1 (3%)
DILATATION/DUCTS	1 (2%)	4 (12%)	2 (5%)	1 (3%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
NECROSIS, FOCAL			1 (3%)	
HYPERPLASIA, EPITHELIAL		3 (9%)	12 (30%)	10 (26%)
HYPERPLASIA, FOCAL	2 (5%)	1 (3%)		
METAPLASIA, SQUAMOUS		1 (3%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY		1 (2%)		
*ABDOMINAL MUSCLE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL			2 (4%)	
FIBROSIS, FOCAL		1 (2%)		
*MUSCLE OF LEG	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
FIBROSIS, MULTIFOCAL		1 (2%)		
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
VEGETABLE FOREIGN BODY		1 (2%)		
HEMORRHAGE	3 (6%)		2 (4%)	1 (2%)
INFLAMMATION, ACUTE FOCAL				2 (4%)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				1 (2%)
NECROSIS, FOCAL		1 (2%)		
FOREIGN MATERIAL, NOS				1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)		
*PLEURA	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
INFLAMMATION, CHRONIC FOCAL				1 (2%)
*MEDIASTINAL PLEURA	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
*PERICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
*EPICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	5 (10%)	1 (2%)	1 (2%)	1 (2%)
AMYLOIDOSIS	1 (2%)			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)		
SPECIAL MORPHOLOGY SUMMARY				
NONE				

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

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
DERMAL INCLUSION CYST			1 (2%)	
ULCER, NOS		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)		
HYPERKERATOSIS		1 (2%)		
ACANTHOSIS		1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)		
FIBROSIS, FOCAL				1 (2%)
RESPIRATORY SYSTEM				
#TRACHEA	(47)	(49)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE				1 (2%)
#TRACHEAL GLAND	(47)	(49)	(50)	(50)
INFLAMMATION, ACUTE FOCAL				1 (2%)
#LUNG/BRONCHUS	(50)	(47)	(50)	(50)
FOREIGN MATERIAL, NOS	2 (4%)			
#LUNG	(50)	(47)	(50)	(50)
EMPHYSEMA, NOS			1 (2%)	
CONGESTION, NOS	1 (2%)			
CONGESTION, ACUTE PASSIVE	1 (2%)		1 (2%)	
EDEMA, NOS		1 (2%)		
HEMORRHAGE	7 (14%)	3 (6%)	4 (8%)	5 (10%)
HEMORRHAGE, CHRONIC				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)			
INFLAMMATION, INTERSTITIAL	1 (2%)			1 (2%)
PNEUMONIA, ASPIRATION	2 (4%)			1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC				3 (6%)
PNEUMONIA INTERSTITIAL CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)			
NECROSIS, FOCAL				1 (2%)
HEMOSIDEROSIS	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	1 (2%)	9 (18%)	6 (12%)
HISTIOCYTOSIS	2 (4%)		1 (2%)	1 (2%)
#LUNG/ALVEOLI	(50)	(47)	(50)	(50)
HEMORRHAGE	1 (2%)			
HEMATOPOIETIC SYSTEM				
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
MASTOCYTOSIS		1 (2%)		
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LEUKEMOID REACTION				1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)	1 (2%)
#BONE MARROW	(49)	(49)	(50)	(50)
HEMORRHAGE		1 (2%)		
NECROSIS, FOCAL			1 (2%)	
HEMOSIDEROSIS		1 (2%)	2 (4%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM				
#BONE MARROW (Continued)	(49)	(49)	(50)	(50)
HYPOPLASIA, NOS		6 (12%)	5 (10%)	1 (2%)
HYPERPLASIA, HEMATOPOIETIC	3 (6%)	14 (29%)	8 (16%)	13 (26%)
HYPERPLASIA, GRANULOCYTIC				1 (2%)
HEMATOPOIESIS		1 (2%)		2 (4%)
#SPLEEN	(49)	(49)	(50)	(49)
HEMORRHAGE				1 (2%)
AMYLOIDOSIS				1 (2%)
HEMOSIDEROSIS			1 (2%)	
LYMPHOID DEPLETION	1 (2%)	2 (4%)		4 (8%)
HYPERPLASIA, LYMPHOID	7 (14%)	4 (8%)	6 (12%)	5 (10%)
HEMATOPOIESIS	5 (10%)	10 (20%)	6 (12%)	13 (27%)
#SPLENIC RED PULP	(49)	(49)	(50)	(49)
HEMATOPOIESIS	4 (8%)			1 (2%)
#LYMPH NODE	(46)	(43)	(39)	(45)
HEMORRHAGE		1 (2%)		
#MANDIBULAR L. NODE	(46)	(43)	(39)	(45)
CYST, NOS		1 (2%)		
HEMORRHAGE	2 (4%)			2 (4%)
AMYLOIDOSIS				1 (2%)
ANGIECTASIS				1 (2%)
HYPERPLASIA, PLASMA CELL			1 (3%)	
HYPERPLASIA, LYMPHOID	4 (9%)	3 (7%)	4 (10%)	4 (9%)
HEMATOPOIESIS				1 (2%)
#BRONCHIAL LYMPH NODE	(46)	(43)	(39)	(45)
HEMORRHAGE	1 (2%)			
#MEDIASTINAL L. NODE	(46)	(43)	(39)	(45)
HYPERPLASIA, LYMPHOID			3 (8%)	
#PANCREATIC L. NODE	(46)	(43)	(39)	(45)
HEMORRHAGE				1 (2%)
NECROSIS, FOCAL				1 (2%)
ANGIECTASIS			1 (3%)	
HYPERPLASIA, PLASMA CELL		1 (2%)		
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)		
#LUMBAR LYMPH NODE	(46)	(43)	(39)	(45)
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HYPERPLASIA, LYMPHOID			1 (3%)	
#MESENTERIC L. NODE	(46)	(43)	(39)	(45)
HEMORRHAGE				1 (2%)
ANGIECTASIS		2 (5%)	1 (3%)	1 (2%)
HYPERPLASIA, PLASMA CELL		1 (2%)		
HYPERPLASIA, RETICULUM CELL			1 (3%)	
HEMATOPOIESIS		1 (2%)	1 (3%)	2 (4%)
#RENAL LYMPH NODE	(46)	(43)	(39)	(45)
ANGIECTASIS		1 (2%)		
HEMATOPOIESIS	1 (2%)			
#THYMIC LYMPH NODE	(46)	(43)	(39)	(45)
CYST, NOS			1 (3%)	
HISTIOCYTOSIS	1 (2%)			
HYPERPLASIA, RETICULUM CELL				1 (2%)
HYPERPLASIA, LYMPHOID			1 (3%)	
HEMATOPOIESIS	1 (2%)			
*FEMUR	(50)	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)			
#LIVER	(50)	(49)	(50)	(50)
HEMATOPOIESIS	3 (6%)	8 (16%)	5 (10%)	3 (6%)
#PEYER'S PATCH	(40)	(42)	(44)	(41)
HYPERPLASIA, LYMPHOID				1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE *TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)*

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#KIDNEY	(50)	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)	
#KIDNEY/MEDULLA	(50)	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
#ADRENAL	(50)	(49)	(50)	(49)
HEMATOPOIESIS	1 (2%)			
#THYMUS	(44)	(40)	(34)	(32)
LYMPHOID DEPLETION				1 (3%)
HYPERPLASIA, LYMPHOID	5 (11%)		3 (9%)	1 (3%)
#THYMIC CORTEX	(44)	(40)	(34)	(32)
NECROSIS, DIFFUSE		2 (5%)		
LYMPHOID DEPLETION	1 (2%)			2 (6%)
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)
#HEART	(50)	(50)	(50)	(49)
MINERALIZATION			1 (2%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
#AURICULAR APPENDAGE	(50)	(50)	(50)	(49)
INFLAMMATION, ACUTE FOCAL				1 (2%)
#RIGHT ATRIUM	(50)	(50)	(50)	(49)
MINERALIZATION			1 (2%)	
INFLAMMATION, ACUTE FOCAL				1 (2%)
FIBROSIS, MULTIFOCAL			1 (2%)	
#LEFT ATRIUM	(50)	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
#RIGHT VENTRICLE	(50)	(50)	(50)	(49)
DEGENERATION, NOS				1 (2%)
#LEFT VENTRICLE	(50)	(50)	(50)	(49)
THROMBUS, MURAL		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)	
FIBROSIS, MULTIFOCAL				1 (2%)
#MYOCARDIUM	(50)	(50)	(50)	(49)
MINERALIZATION				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	3 (6%)			
DEGENERATION, NOS	1 (2%)			1 (2%)
#CARDIAC VALVE	(50)	(50)	(50)	(49)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
PIGMENTATION, NOS				1 (2%)
#TRICUSPID VALVE	(50)	(50)	(50)	(49)
PIGMENTATION, NOS	1 (2%)			
#MITRAL VALVE	(50)	(50)	(50)	(49)
PIGMENTATION, NOS	1 (2%)			
*BLOOD VESSEL	(50)	(50)	(50)	(50)
NECROSIS, FIBRINOID		1 (2%)		
*ARTERY	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
*AORTA	(50)	(50)	(50)	(50)
THROMBOSIS, NOS	2 (4%)			
*UTERINE ARTERY	(50)	(50)	(50)	(50)
CONGENITAL MALFORMATION, NOS			1 (2%)	
*VEIN	(50)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	
*PULMONARY VEIN	(50)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	
#UTERUS	(50)	(49)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(47)	(47)	(49)	(47)
INFLAMMATION, MULTIFOCAL	3 (6%)			
INFLAMMATION, CHRONIC FOCAL	10 (21%)	7 (15%)	11 (22%)	7 (15%)
#LIVER	(50)	(49)	(50)	(50)
CONGESTION, CHRONIC PASSIVE				2 (4%)
HEMORRHAGE	1 (2%)			
HEMORRHAGIC CYST		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (4%)	1 (2%)
DEGENERATION, LIPOID			1 (2%)	
NECROSIS, FOCAL	3 (6%)			1 (2%)
NECROSIS, COAGULATIVE		2 (4%)	2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION		3 (6%)		
FOCAL CELLULAR CHANGE	1 (2%)		1 (2%)	
CYTOLOGIC ALTERATION, NOS	1 (2%)			
CELL-SIZE, ALTERATION	1 (2%)	1 (2%)	3 (6%)	3 (6%)
ATROPHY, DIFFUSE			1 (2%)	
ANGIECTASIS			1 (2%)	
#LIVER/CAUDATE LOBE	(50)	(49)	(50)	(50)
INFARCT HEMORRHAGIC				1 (2%)
#LIVER/CENTRILOBULAR	(50)	(49)	(50)	(50)
NECROSIS, FOCAL	1 (2%)			
#LIVER/HEPATOCYTES	(50)	(49)	(50)	(50)
NECROSIS, FOCAL				2 (4%)
NECROSIS, COAGULATIVE				1 (2%)
CYTOPLASMIC VACUOLIZATION				2 (4%)
*GALLBLADDER	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	3 (6%)			1 (2%)
#PANCREAS	(47)	(46)	(48)	(43)
DILATATION/DUCTS			2 (4%)	
CYST, NOS			1 (2%)	
CYSTIC DUCTS	1 (2%)			
INFLAMMATION, MULTIFOCAL	1 (2%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	3 (6%)	3 (7%)	1 (2%)	
NECROSIS, FOCAL				1 (2%)
AMYLOIDOSIS				1 (2%)
ATROPHY, FOCAL				2 (5%)
#PANCREATIC DUCT	(47)	(46)	(48)	(43)
RETENTION OF CONTENT			1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)	
#PANCREATIC ACINUS	(47)	(46)	(48)	(43)
ATROPHY, FOCAL	3 (6%)		3 (6%)	
ATROPHY, DIFFUSE	1 (2%)	1 (2%)	3 (6%)	1 (2%)
#PERIPANCREATIC TISSUE	(47)	(46)	(48)	(43)
NECROSIS, FAT	1 (2%)			
#ESOPHAGUS	(49)	(47)	(48)	(49)
DILATATION, NOS				1 (2%)
#PERIESOPHAGEAL TISSUE	(49)	(47)	(48)	(49)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
#STOMACH	(43)	(45)	(45)	(43)
INFLAMMATION, FOCAL	1 (2%)			
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	4 (9%)			
EROSION				1 (2%)
HYPERKERATOSIS				1 (2%)
#GASTRIC MUCOSA	(43)	(45)	(45)	(43)
CRYSTALS, NOS				1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#GASTRIC FUNDAL GLAND	(43)	(45)	(45)	(43)
DILATATION, NOS		4 (9%)	1 (2%)	4 (9%)
#GLANDULAR STOMACH	(43)	(45)	(45)	(43)
DILATATION, NOS			1 (2%)	
#GASTRIC SUBMUCOSA	(43)	(45)	(45)	(43)
EDEMA, NOS	1 (2%)			
#CARDIAC STOMACH	(43)	(45)	(45)	(43)
MINERALIZATION				1 (2%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	3 (7%)	6 (13%)	6 (14%)
HYPERKERATOSIS		1 (2%)	5 (11%)	7 (16%)
#GASTRIC FUNDUS	(43)	(45)	(45)	(43)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		2 (4%)		
NECROSIS, FOCAL			1 (2%)	2 (5%)
HYPERPLASIA, FOCAL				1 (2%)
HYPERPLASIA, DIFFUSE				1 (2%)
#PEYER'S PATCH	(40)	(42)	(44)	(41)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
NECROSIS, COAGULATIVE			1 (2%)	
#COLON	(49)	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
PARASITISM	1 (2%)	2 (4%)		4 (8%)
NECROSIS, FOCAL			1 (2%)	
HYPERPLASIA, DIFFUSE			1 (2%)	
#CECUM	(49)	(49)	(50)	(49)
PARASITISM				1 (2%)
HYPERPLASIA, DIFFUSE			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(49)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	1 (2%)	1 (2%)	
GLOMERULONEPHRITIS, MEMBRANOUS				2 (4%)
GLOMERULONEPHRITIS, SUBACUTE		2 (4%)		
GLOMERULONEPHRITIS, CHRONIC	1 (2%)			1 (2%)
NEPHROPATHY	1 (2%)	4 (8%)	7 (14%)	2 (4%)
NEPHROSIS, NOS		1 (2%)		
GLOMERULOSCLEROSIS, NOS				1 (2%)
INFARCT, FOCAL		1 (2%)	1 (2%)	2 (4%)
#RENAL PAPILLA	(50)	(49)	(50)	(50)
NECROSIS, FOCAL				1 (2%)
#PERIRENAL TISSUE	(50)	(49)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		1 (2%)
#KIDNEY/TUBULE	(50)	(49)	(50)	(50)
CYST, NOS			1 (2%)	
NEPHROPATHY				1 (2%)
DEGENERATION, NOS	1 (2%)			1 (2%)
PIGMENTATION, NOS				1 (2%)
ATROPHY, FOCAL				1 (2%)
REGENERATION, NOS	1 (2%)			1 (2%)
#URINARY BLADDER	(40)	(45)	(45)	(40)
INFLAMMATION, CHRONIC FOCAL	7 (18%)	11 (24%)	15 (33%)	11 (28%)
ANGIECTASIS	1 (3%)			

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(46)	(39)	(45)	(35)
HEMORRHAGE				1 (3%)
HEMORRHAGIC CYST				1 (3%)
HYPERPLASIA, FOCAL	9 (20%)	5 (13%)	4 (9%)	3 (9%)
#ANTERIOR PITUITARY	(46)	(39)	(45)	(35)
CONGESTION, NOS	1 (2%)			
ANGIECTASIS	1 (2%)	1 (3%)		
#ADRENAL	(50)	(49)	(50)	(49)
HEMORRHAGE		1 (2%)		
ATROPHY, DIFFUSE				1 (2%)
#ADRENAL/CAPSULE	(50)	(49)	(50)	(49)
INFLAMMATION, ACUTE FOCAL	1 (2%)			
HYPERPLASIA, NOS		1 (2%)		
HYPERPLASIA, FOCAL	5 (10%)	18 (37%)	34 (68%)	30 (61%)
#ADRENAL CORTEX	(50)	(49)	(50)	(49)
CYST, NOS			2 (4%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC FOCAL		2 (4%)		
DEGENERATION, NOS				4 (8%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	1 (2%)		
FOCAL CELLULAR CHANGE	2 (4%)	10 (20%)	5 (10%)	3 (6%)
CYTOPLASMIC MATRIX, ALTERATION	2 (4%)			
CELL-SIZE, ALTERATION			1 (2%)	1 (2%)
HYPERTROPHY, FOCAL	1 (2%)			
HYPERPLASIA, FOCAL				1 (2%)
#ADRENAL MEDULLA	(50)	(49)	(50)	(49)
CYST, NOS			1 (2%)	
FIBROSIS, MULTIFOCAL			1 (2%)	
HYPERPLASIA, FOCAL	15 (30%)	3 (6%)	4 (8%)	3 (6%)
#PERIADRENAL TISSUE	(50)	(49)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL	2 (4%)			
#THYROID	(49)	(46)	(48)	(47)
FOREIGN BODY, NOS			1 (2%)	
CYST, NOS	1 (2%)			1 (2%)
FOLLICULAR CYST, NOS		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)		1 (2%)
HYPERPLASIA, CYSTIC				1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	7 (14%)	2 (4%)	6 (13%)	3 (6%)
#THYROID FOLLICLE	(49)	(46)	(48)	(47)
HYPERPLASIA, CYSTIC		2 (4%)		
#PARATHYROID	(15)	(19)	(17)	(24)
EMBRYONAL DUCT CYST		1 (5%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (5%)		
#PANCREATIC ISLETS	(47)	(46)	(48)	(43)
HYPERPLASIA, FOCAL	3 (6%)		1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		2 (4%)		
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
HYPERPLASIA, FOCAL			1 (2%)	
HYPERPLASIA, CYSTIC	2 (4%)	4 (8%)	1 (2%)	1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#CLITORAL GLAND	(23)	(21)	(15)	(9)
INFLAMMATION, MULTIFOCAL				1 (11%)
INFLAMMATION, ACUTE FOCAL	1 (4%)	1 (5%)		
INFLAMMATION, ACUTE DIFFUSE	1 (4%)		1 (7%)	
INFLAMMATION, ACUTE/CHRONIC	2 (9%)			
INFLAMMATION, CHRONIC FOCAL	2 (9%)	6 (29%)	4 (27%)	2 (22%)
INFLAMMATION, CHRONIC DIFFUSE	1 (4%)		1 (7%)	
HYPERPLASIA, EPITHELIAL		6 (29%)	2 (13%)	1 11%)
HYPERKERATOSIS		1 (5%)		
METAPLASIA, SQUAMOUS			1 (7%)	
#UTERUS	(50)	(49)	(50)	(50)
DILATATION, NOS	1 (2%)			
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)	
INFLAMMATION, MULTIFOCAL			1 (2%)	
PYOMETRA	1 (2%)	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)			1 (2%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	3 (6%)	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
FIBROSIS, FOCAL	1 (2%)	2 (4%)		1 (2%)
FIBROSIS, MULTIFOCAL		2 (4%)		3 (6%)
DEPOSIT, NOS	1 (2%)			
ANGIECTASIS		1 (2%)		2 (4%)
#CERVIX UTERI	(50)	(49)	(50)	(50)
CYST, NOS		1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)	(50)
CYST, NOS			1 (2%)	
MULTIPLE CYSTS				1 (2%)
HEMORRHAGE	2 (4%)			
INFLAMMATION, NECROTIZING	1 (2%)			
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
HYPERPLASIA, EPITHELIAL				1 (2%)
HYPERPLASIA, FOCAL	3 (6%)		2 (4%)	1 (2%)
HYPERPLASIA, CYSTIC	39 (78%)	35 (71%)	41 (82%)	29 (58%)
METAPLASIA, SQUAMOUS	2 (4%)			
#OVARY/PAROVARIAN	(48)	(49)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
#OVARY	(48)	(49)	(49)	(49)
MINERALIZATION		1 (2%)	1 (2%)	1 (2%)
CYST, NOS	8 (17%)	8 (16%)	8 (16%)	5 (10%)
MULTIPLE CYSTS		7 (14%)	6 (12%)	3 (6%)
PAROVARIAN CYST	2 (4%)		1 (2%)	2 (4%)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)	1 (2%)
HEMORRHAGIC CYST	7 (15%)	2 (4%)	2 (4%)	2 (4%)
ABSCESS, NOS				1 (2%)
NECROSIS, FOCAL			1 (2%)	
ATROPHY, SENILE	15 (31%)	35 (71%)	32 (65%)	22 (45%)
HYPERPLASIA, EPITHELIAL	12 (25%)	39 (80%)	31 (63%)	29 (59%)
ANGIECTASIS			3 (6%)	4 (8%)
#OVARY/FOLLICLE	(48)	(49)	(49)	(49)
MULTIPLE CYSTS				1 (2%)
NERVOUS SYSTEM				
#LATERAL VENTRICLE	(49)	(50)	(50)	(49)
DILATATION, NOS		1 (2%)		
#CEREBRUM	(49)	(50)	(50)	(49)
HEMORRHAGE				1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
NERVOUS SYSMTEM (Continued)				
#BRAIN	(49)	(50)	(50)	(49)
HYDROCEPHALUS, NOS				1 (2%)
CONGESTION, NOS	1 (2%)			
HEMORRHAGE	1 (2%)			
ATROPHY, PRESSURE			1 (2%)	
#BRAIN/THALAMUS	(49)	(50)	(50)	(49)
COMPRESSION				1 (2%)
MINERALIZATION	18 (37%)	13 (26%)	25 (50%)	14 (29%)
SPECIAL SENSE ORGANS				
*EYE/CORNEA	(50)	(50)	(50)	(50)
ULCER, NOS			1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)			
PIGMENTATION, NOS	1 (2%)			
SPECIAL SENSE ORGANS (Continued)				
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)	(50)
DISPLACEMENT, NOS	1 (2%)			
#HARDERIAN GLAND	(49)	(49)	(50)	(48)
INFLAMMATION, FOCAL			1 (2%)	1 (2%)
INFLAMMATION, MULTIFOCAL	1 (2%)		1 (2%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	16 (33%)	15 (31%)	11 (22%)	7 (15%)
FIBROSIS, DIFFUSE				1 (2%)
PIGMENTATION, NOS	1 (2%)			
ATROPHY, FOCAL	1 (2%)			
ATROPHY, DIFFUSE		1 (2%)		
HYPERPLASIA, FOCAL	5 (10%)	10 (20%)	11 (22%)	9 (19%)
HYPERPLASIA, DIFFUSE	1 (2%)			1 (2%)
#ZYMBAL GLAND	(43)	(33)	(37)	(31)
DILATATION, NOS		1 (3%)		
DILATATION/DUCTS		1 (3%)		
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (3%)	2 (5%)	6 (19%)
HYPERPLASIA, FOCAL				1 (3%)
HYPERPLASIA, DIFFUSE			2 (5%)	
HYPERKERATOSIS			1 (3%)	
METAPLASIA, SQUAMOUS			1 (3%)	
PARAKERATOSIS	1 (2%)			
MUSCULOSKELETAL SYSTEM				
*FEMUR	(50)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY	32 (64%)	33 (66%)	38 (76%)	25 (50%)
*ABDOMINAL MUSCLE	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
FIBROSIS	1 (2%)			
*MUSCLE OF LEG	(50)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	CONTROL (VEH)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS	2 (4%)			
HEMORRHAGE	3 (6%)		2 (4%)	
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)			2 (4%)
FOREIGN MATERIAL, NOS	3 (6%)			
*ABDOMINAL CAVITY	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)		
NECROSIS, FAT		1 (2%)		
FOREIGN MATERIAL, NOS	1 (2%)			
*PLEURA	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)	1 (2%)
*EPICARDIUM	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)	
*MESENTERY	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
INFLAMMATION ACTIVE CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR				1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL	14 (28%)		4 (8%)	3 (6%)
AMYLOIDOSIS				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, FOCAL			2 (4%)	1 (2%)
PERIORBITAL REGION				
INFLAMMATION, ACUTE/CHRONIC		1		
ADIPOSE TISSUE				
INFLAMMATION, CHRONIC FOCAL			1	
CYTOPLASMIC VACUOLIZATION				1
SPECIAL MORPHOLOGY SUMMARY				
AUTO/NECROPSY/HISTO PERF		1		

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Skin: Squamous Cell Papilloma				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	0.0%	6.9%	4.0%	27.1%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests (d)	P=0.001	P=0.216	P=0.451	P=0.005
Incidental Tumor Tests (d)	P=0.002	P=0.216	P=0.451	P=0.009
Cochran-Armitage Trend Test (d)	P=0.014			
Fisher Exact Tests		P=0.247	P=0.500	P=0.028
Skin: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	5/50 (10%)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	0.0%	15.3%	9.8%	30.3%
Terminal Rates (c)	0/32 (0%)	3/29 (10%)	0/25 (0%)	2/16 (13%)
Life Table Tests (d)	P<0.001	P=0.032	P=0.098	P=0.001
Incidental Tumor Tests (d)	P=0.069	P=0.064	P=0.278	P=0.039
Cochran-Armitage Trend Test (d)	P=0.007			
Fisher Exact Tests		P=0.028	P=0.121	P=0.003
Skin: All Squamous Cell Tumors				
Overall Rates (a)	1/50 (2%)	7/50 (14%)	5/50 (10%)	11/50 (22%)
Adjusted Rates (b)	2.7%	21.8%	17.0%	45.2%
Terminal Rates (c)	0/32 (0%)	5/29 (17%)	2/25 (8%)	5/16 (31%)
Life Table Tests (d)	P<0.001	P=0.031	P=0.076	P<0.001
Incidental Tumor Tests (d)	P=0.017	P=0.055	P=0.221	P=0.012
Cochran-Armitage Trend Test (d)	P=0.004			
Fisher Exact Tests		P=0.030	P=0.102	P=0.002
Skin: Squamous Cell Tumors or Undifferentiated Carcinoma				
Overall Rates (a)	1/50 (2%)	7/50 (14%)	5/50 (10%)	12/50 (24%)
Adjusted Rates (b)	2.7%	21.8%	17.0%	47.7%
Terminal Rates (c)	0/32 (0%)	5/29 (17%)	2/25 (8%)	5/16 (31%)
Life Table Tests (d)	P<0.001	P=0.031	P=0.076	P<0.001
Incidental Tumor Tests (d)	P=0.010	P=0.055	P=0.221	P=0.009
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Tests		P=0.030	P=0.102	P<0.001
Skin: Sebaceous Adenoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.4%	8.0%	0.0%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	2/25 (8%)	0/16 (0%)
Life Table Tests (d)	P=0.617N	P=0.114	P=0.185	(e)
Incidental Tumor Tests (d)	P=0.505N	P=0.166	P=0.185	(e)
Cochran-Armitage Trend Test (d)	P=0.409N			
Fisher Exact Tests		P=0.121	P=0.247	(e)
Skin: Trichoepithelioma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	0.0%	10.3%	4.0%	2.3%
Terminal Rates (c)	0/32 (0%)	3/29 (10%)	1/25 (4%)	0/16 (0%)
Life Table Tests (d)	P=0.426	P=0.103	P=0.451	P=0.530
Incidental Tumor Tests (d)	P=0.531	P=0.103	P=0.451	P=0.785
Cochran-Armitage Trend Test (d)	P=0.591			
Fisher Exact Tests		P=0.121	P=0.500	P=0.500
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	12.5%	6.1%	12.0%	20.5%
Terminal Rates (c)	4/32 (13%)	1/29 (3%)	3/25 (12%)	3/16 (19%)
Life Table Tests (d)	P=0.184	P=0.371N	P=0.636N	P=0.312
Incidental Tumor Tests (d)	P=0.221	P=0.295N	P=0.636N	P=0.280
Cochran-Armitage Trend Test (d)	P=0.481			
Fisher Exact Tests		P=0.339N	P=0.500N	P=0.643

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.4%	2.9%	4.0%	11.1%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	1/25 (4%)	1/16 (6%)
Life Table Tests (d)	P=0.102	P=0.749N	P=0.752	P=0.272
Incidental Tumor Tests (d)	P=0.284	P=0.616N	P=0.718N	P=0.446
Cochran-Armitage Trend Test (d)	P=0.163			
Fisher Exact Tests		P=0.753	P=0.753	P=0.309
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	5/50 (10%)	3/50 (6%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	14.6%	8.7%	16.0%	30.4%
Terminal Rates (c)	4/32 (13%)	1/29 (3%)	4/25 (16%)	4/16 (25%)
Life Table Tests (d)	P=0.048	P=0.382N	P=0.626N	P=0.139
Incidental Tumor Tests (d)	P=0.125	P=0.241N	P=0.592N	P=0.181
Cochran-Armitage Trend Test (d)	P=0.219			
Fisher Exact Tests		P=0.357N	P=0.500N	P=0.380
Integumentary System: Fibrosarcoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.4%	2.9%	8.0%	11.1%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	2/25 (8%)	1/16 (6%)
Life Table Tests (d)	P=0.089	P=0.749N	P=0.461	P=0.272
Incidental Tumor Tests (d)	P=0.243	P=0.616N	P=0.521	P=0.446
Cochran-Armitage Trend Test (d)	P=0.165			
Fisher Exact Tests		P=0.753	P=0.500	P=0.309
Integumentary System: Fibroma or Fibrosarcoma				
Overall Rates (a)	5/50 (10%)	3/50 (6%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	14.6%	8.7%	20.0%	30.4%
Terminal Rates (c)	4/32 (13%)	1/29 (3%)	5/25 (20%)	4/16 (25%)
Life Table Tests (d)	P=0.041	P=0.382N	P=0.496	P=0.139
Incidental Tumor Tests (d)	P=0.109	P=0.241N	P=0.531	P=0.181
Cochran-Armitage Trend Test (d)	P=0.213			
Fisher Exact Tests		P=0.357N	P=0.630	P=0.380
Subcutaneous Tissue: Fibroma, Neurofibroma, Fibrosarcoma, or Neurofibroma				
Overall Rates (a)	6/50 (12%)	4/50 (8%)	4/50 (8%)	7/50 (14%)
Adjusted Rates (b)	17.7%	12.0%	16.0%	30.4%
Terminal Rates (c)	5/32 (16%)	2/29 (7%)	4/25 (16%)	4/16 (25%)
Life Table Tests (d)	P=0.096	P=0.405N	P=0.504N	P=0.198
Incidental Tumor Tests (d)	P=0.212	P=0.274N	P=0.469N	P=0.253
Cochran-Armitage Trend Test (d)	P=0.363			
Fisher Exact Tests		P=0.370N	P=0.370N	P=0.500
Integumentary System: Fibroma, Neurofibroma, Fibrosarcoma, or Neurofibroma				
Overall Rates (a)	6/50 (12%)	4/50 (8%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	17.7%	12.0%	20.0%	30.4%
Terminal Rates (c)	5/32 (16%)	2/29 (7%)	5/25 (20%)	4/16 (25%)
Life Table Tests (d)	P=0.084	P=0.405N	P=0.610	P=0.198
Incidental Tumor Tests (d)	P=0.188	P=0.274N	P=0.616N	P=0.253
Cochran-Armitage Trend Test (d)	P=0.351			
Fisher Exact Tests		P=0.370N	P=0.500N	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	7/50 (14%)	2/50 (4%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	17.5%	6.5%	15.3%	23.6%
Terminal Rates (c)	2/32 (6%)	1/29 (3%)	3/25 (12%)	1/16 (6%)
Life Table Tests (d)	P=0.239	P=0.100N	P=0.379N	P=0.472
Incidental Tumor Tests (d)	P=0.453N	P=0.045N	P=0.322N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.516			
Fisher Exact Tests		P=0.080N	P=0.262N	P=0.500N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Palate: Squamous Cell Papilloma				
Overall Rates (a)	0/50 (0%)	4/50 (8%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	0.0%	11.4%	11.7%	37.8%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests (d)	P<0.001	P=0.064	P=0.057	P<0.001
Incidental Tumor Tests (d)	P=0.005	P=0.098	P=0.142	P=0.006
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Tests		P=0.059	P=0.059	P=0.001
Palate: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	0/50 (0%)	4/50 (8%)	5/50 (10%)	9/50 (18%)
Adjusted Rates (b)	0.0%	11.4%	13.6%	37.8%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	1/25 (4%)	4/16 (25%)
Life Table Tests (d)	P<0.001	P=0.064	P=0.034	P<0.001
Incidental Tumor Tests (d)	P=0.005	P=0.098	P=0.097	P=0.006
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Tests		P=0.059	P=0.028	P=0.001
Lip: Squamous Cell Papilloma				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	0.0%	6.9%	20.0%	23.9%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	5/25 (20%)	3/16 (19%)
Life Table Tests (d)	P=0.001	P=0.216	P=0.015	P=0.008
Incidental Tumor Tests (d)	P=0.004	P=0.216	P=0.015	P=0.027
Cochran-Armitage Trend Test (d)	P=0.022			
Fisher Exact Tests		P=0.247	P=0.028	P=0.028
Lip: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	17.4%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	0/25 (0%)	2/16 (13%)
Life Table Tests (d)	P=0.002	(e)	(e)	P=0.035
Incidental Tumor Tests (d)	P=0.008	(e)	(e)	P=0.091
Cochran-Armitage Trend Test (d)	P=0.012			
Fisher Exact Tests		(e)	(e)	P=0.121
Lip: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (b)	0.0%	6.9%	20.0%	39.2%
Terminal Rates (c)	0/32 (0%)	2/29 (7%)	5/25 (20%)	5/16 (31%)
Life Table Tests (d)	P<0.001	P=0.216	P=0.015	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.216	P=0.015	P=0.002
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Tests		P=0.247	P=0.028	P=0.003
Tongue: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	7.4%	12.8%	17.2%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	2/25 (8%)	2/16 (13%)
Life Table Tests (d)	P=0.039	P=0.133	P=0.051	P=0.028
Incidental Tumor Tests (d)	P=0.049	P=0.133	P=0.099	P=0.012
Cochran-Armitage Trend Test (d)	P=0.078			
Fisher Exact Tests		P=0.121	P=0.059	P=0.059
Tongue: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	6/50 (12%)	6/50 (12%)
Adjusted Rates (b)	2.3%	7.4%	20.4%	24.7%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	4/25 (16%)	3/16 (19%)
Life Table Tests (d)	P=0.013	P=0.328	P=0.044	P=0.028
Incidental Tumor Tests (d)	P=0.012	P=0.355	P=0.091	P=0.009
Cochran-Armitage Trend Test (d)	P=0.039			
Fisher Exact Tests		P=0.309	P=0.056	P=0.056

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (*Continued*)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Oral Cavity: Squamous Cell Papilloma				
Overall Rates (a)	1/50 (2%)	6/50 (12%)	11/50 (22%)	13/50 (26%)
Adjusted Rates (b)	2.3%	18.0%	37.4%	47.7%
Terminal Rates (c)	0/32 (0%)	4/29 (14%)	8/25 (32%)	5/16 (31%)
Life Table Tests (d)	P<0.001	P=0.058	P=0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.083	P=0.004	P=0.002
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.056	P=0.002	P<0.001
Oral Cavity: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	0.0%	7.4%	14.7%	33.0%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	2/25 (8%)	4/16 (25%)
Life Table Tests (d)	P=0.001	P=0.133	P=0.030	P=0.001
Incidental Tumor Tests (d)	P=0.002	P=0.133	P=0.071	P=0.001
Cochran-Armitage Trend Test (d)	P=0.006			
Fisher Exact Tests		P=0.121	P=0.028	P=0.006
Oral Cavity: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	1/50 (2%)	9/50 (18%)	16/50 (32%)	19/50 (38%)
Adjusted Rates (b)	2.3%	24.1%	48.8%	68.6%
Terminal Rates (c)	0/32 (0%)	4/29 (14%)	10/25 (40%)	9/16 (56%)
Life Table Tests (d)	P<0.001	P=0.012	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.014	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.008	P<0.001	P<0.001
Liver: Neoplastic Nodule				
Overall Rates (a)	2/50 (4%)	2/48 (4%)	4/49 (8%)	1/49 (2%)
Adjusted Rates (b)	6.0%	6.9%	14.7%	6.3%
Terminal Rates (c)	1/32 (3%)	2/29 (7%)	3/24 (13%)	1/16 (6%)
Life Table Tests (d)	P=0.503	P=0.662	P=0.235	P=0.725N
Incidental Tumor Tests (d)	P=0.524N	P=0.641N	P=0.364	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.436N			
Fisher Exact Tests		P=0.676	P=0.329	P=0.508N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	2/50 (4%)	2/48 (4%)	5/49 (10%)	1/49 (2%)
Adjusted Rates (b)	6.0%	6.9%	18.8%	6.3%
Terminal Rates (c)	1/32 (3%)	2/29 (7%)	4/24 (17%)	1/16 (6%)
Life Table Tests (d)	P=0.445	P=0.662	P=0.131	P=0.725N
Incidental Tumor Tests (d)	P=0.579N	P=0.641N	P=0.217	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.461N			
Fisher Exact Tests		P=0.676	P=0.210	P=0.508N
Pancreas: Acinar Cell Adenoma				
Overall Rates (a)	5/49 (10%)	1/44 (2%)	3/47 (6%)	0/49 (0%)
Adjusted Rates (b)	15.6%	3.4%	12.5%	0.0%
Terminal Rates (c)	5/32 (16%)	1/29 (3%)	3/24 (13%)	0/16 (0%)
Life Table Tests (d)	P=0.120N	P=0.124N	P=0.522N	P=0.124N
Incidental Tumor Tests (d)	P=0.120N	P=0.124N	P=0.522N	P=0.124N
Cochran-Armitage Trend Test (d)	P=0.036N			
Fisher Exact Tests		P=0.128N	P=0.381N	P=0.028N
Pituitary: Adenoma				
Overall Rates (a)	14/47 (30%)	11/45 (24%)	11/46 (24%)	7/48 (15%)
Adjusted Rates (b)	39.3%	34.1%	35.6%	24.9%
Terminal Rates (c)	11/32 (34%)	8/28 (29%)	6/24 (25%)	1/16 (6%)
Life Table Tests (d)	P=0.362N	P=0.417N	P=0.553N	P=0.340N
Incidental Tumor Tests (d)	P=0.026N	P=0.323N	P=0.229N	P=0.036N
Cochran-Armitage Trend Test (d)	P=0.051N			
Fisher Exact Tests		P=0.367N	P=0.343N	P=0.061N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Pituitary: Carcinoma				
Overall Rates (a)	4/47 (9%)	0/45 (0%)	0/46 (0%)	0/48 (0%)
Adjusted Rates (b)	11.5%	0.0%	0.0%	0.0%
Terminal Rates (c)	2/32 (6%)	0/28 (0%)	0/24 (0%)	0/16 (0%)
Life Table Tests (d)	P=0.037N	P=0.074N	P=0.098N	P=0.141N
Incidental Tumor Tests (d)	P=0.007N	P=0.044N	P=0.028N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.020N			
Fisher Exact Tests		P=0.064N	P=0.061N	P=0.056N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	18/47 (38%)	11/45 (24%)	11/46 (24%)	7/48 (15%)
Adjusted Rates (b)	48.1%	34.1%	35.6%	24.9%
Terminal Rates (c)	13/32 (41%)	8/28 (29%)	6/24 (25%)	1/16 (6%)
Life Table Tests (d)	P=0.154N	P=0.152N	P=0.266N	P=0.142N
Incidental Tumor Tests (d)	P=0.002N	P=0.071N	P=0.038N	P=0.002N
Cochran-Armitage Trend Test (d)	P=0.008N			
Fisher Exact Tests		P=0.114N	P=0.101N	P=0.008N
Adrenal: Pheochromocytoma				
Overall Rates (a)	11/50 (22%)	11/49 (22%)	5/48 (10%)	4/49 (8%)
Adjusted Rates (b)	32.2%	32.2%	16.3%	19.2%
Terminal Rates (c)	9/32 (28%)	7/29 (24%)	3/25 (12%)	2/16 (13%)
Life Table Tests (d)	P=0.156N	P=0.530	P=0.184N	P=0.326N
Incidental Tumor Tests (d)	P=0.015N	P=0.451N	P=0.085N	P=0.060N
Cochran-Armitage Trend Test (d)	P=0.018N			
Fisher Exact Tests		P=0.574	P=0.100N	P=0.049N
Thyroid: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	1/49 (2%)	0/47 (0%)	2/46 (4%)	3/47 (6%)
Adjusted Rates (b)	2.9%	0.0%	8.3%	12.4%
Terminal Rates (c)	0/32 (0%)	0/29 (0%)	2/24 (8%)	1/16 (6%)
Life Table Tests (d)	P=0.040	P=0.489N	P=0.408	P=0.199
Incidental Tumor Tests (d)	P=0.160	P=0.331N	P=0.511	P=0.611
Cochran-Armitage Trend Test (d)	P=0.099			
Fisher Exact Tests		P=0.510N	P=0.476	P=0.293
Thyroid: C-Cell Adenoma				
Overall Rates (a)	7/49 (14%)	4/47 (9%)	1/46 (2%)	2/47 (4%)
Adjusted Rates (b)	21.9%	13.8%	3.7%	10.7%
Terminal Rates (c)	7/32 (22%)	4/29 (14%)	0/24 (0%)	1/16 (6%)
Life Table Tests (d)	P=0.164N	P=0.315N	P=0.072N	P=0.339N
Incidental Tumor Tests (d)	P=0.090N	P=0.315N	P=0.051N	P=0.227N
Cochran-Armitage Trend Test (d)	P=0.042N			
Fisher Exact Tests		P=0.287N	P=0.036N	P=0.090N
Thyroid: C-Cell Carcinoma				
Overall Rates (a)	2/49 (4%)	1/47 (2%)	3/46 (7%)	0/47 (0%)
Adjusted Rates (b)	5.5%	2.8%	11.6%	0.0%
Terminal Rates (c)	1/32 (3%)	0/29 (0%)	2/24 (8%)	0/16 (0%)
Life Table Tests (d)	P=0.381N	P=0.499N	P=0.410	P=0.290N
Incidental Tumor Tests (d)	P=0.219N	P=0.392N	P=0.533	P=0.351N
Cochran-Armitage Trend Test (d)	P=0.253N			
Fisher Exact Tests		P=0.516N	P=0.470	P=0.258N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	9/49 (18%)	5/47 (11%)	4/46 (9%)	2/47 (4%)
Adjusted Rates (b)	26.9%	16.2%	14.9%	10.7%
Terminal Rates (c)	8/32 (25%)	4/29 (14%)	2/24 (8%)	1/16 (6%)
Life Table Tests (d)	P=0.122N	P=0.236N	P=0.238N	P=0.165N
Incidental Tumor Tests (d)	P=0.039N	P=0.196N	P=0.141N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.022N			
Fisher Exact Tests		P=0.217N	P=0.142N	P=0.030N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg
Testis: Interstitial Cell Tumor				
Overall Rates (a)	34/50 (68%)	37/48 (77%)	34/50 (68%)	32/48 (67%)
Adjusted Rates (b)	91.9%	92.4%	94.2%	100.0%
Terminal Rates (c)	29/32 (91%)	26/29 (90%)	23/25 (92%)	16/16 (100%)
Life Table Tests (d)	P=0.002	P=0.170	P=0.092	P=0.002
Incidental Tumor Tests (d)	P=0.555N	P=0.370	P=0.550	P=0.406
Cochran-Armitage Trend Test (d)	P=0.350N			
Fisher Exact Tests		P=0.218	P=0.585N	P=0.530N
Zymbal Gland: Carcinoma				
Overall Rates (a)	2/32 (6%)	6/46 (13%)	10/42 (24%)	17/42 (40%)
Adjusted Rates (b)	7.2%	15.4%	28.8%	55.6%
Terminal Rates (c)	1/22 (5%)	2/28 (7%)	2/21 (10%)	5/15 (33%)
Life Table Tests (d)	P<0.001	P=0.193	P=0.017	P<0.001
Incidental Tumor Tests (d)	P=0.003	P=0.352	P=0.214	P=0.024
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.282	P=0.040	P<0.001
Zymbal Gland: Adenoma or Carcinoma				
Overall Rates (a)	2/32 (6%)	7/46 (15%)	10/42 (24%)	18/42 (43%)
Adjusted Rates (b)	7.2%	18.7%	28.8%	57.0%
Terminal Rates (c)	1/22 (5%)	3/28 (11%)	2/21 (10%)	5/15 (33%)
Life Table Tests (d)	P<0.001	P=0.131	P=0.017	P<0.001
Incidental Tumor Tests (d)	P=0.002	P=0.247	P=0.214	P=0.019
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.197	P=0.040	P<0.001
Tunica Vaginalis: Mesothelioma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.7%	3.4%	6.5%	6.3%
Terminal Rates (c)	2/32 (6%)	1/29 (3%)	1/25 (4%)	1/16 (6%)
Life Table Tests (d)	P=0.425N	P=0.331N	P=0.567N	P=0.483N
Incidental Tumor Tests (d)	P=0.263N	P=0.333N	P=0.407N	P=0.364N
Cochran-Armitage Trend Test (d)	P=0.279N			
Fisher Exact Tests		P=0.309N	P=0.500N	P=0.309N

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

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	6/50 (12%)	7/50 (14%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	12.8%	16.7%	17.1%	31.2%
Terminal Rates (c)	5/46 (11%)	4/38 (11%)	5/34 (15%)	6/25 (24%)
Life Table Tests (d)	P=0.035	P=0.373	P=0.404	P=0.040
Incidental Tumor Tests (d)	P=0.243	P=0.572	P=0.521	P=0.198
Cochran-Armitage Trend Test (d)	P=0.245			
Fisher Exact Tests		P=0.500	P=0.620N	P=0.288
Palate: Squamous Cell Papilloma				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	2.2%	7.9%	13.9%	8.6%
Terminal Rates (c)	1/46 (2%)	3/38 (8%)	4/34 (12%)	1/25 (4%)
Life Table Tests (d)	P=0.103	P=0.240	P=0.053	P=0.183
Incidental Tumor Tests (d)	P=0.183	P=0.240	P=0.101	P=0.620
Cochran-Armitage Trend Test (d)	P=0.273			
Fisher Exact Tests		P=0.309	P=0.102	P=0.309
Palate: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	2.2%	10.2%	13.9%	11.4%
Terminal Rates (c)	1/46 (2%)	3/38 (8%)	4/34 (12%)	1/25 (4%)
Life Table Tests (d)	P=0.060	P=0.131	P=0.053	P=0.088
Incidental Tumor Tests (d)	P=0.219	P=0.153	P=0.101	P=0.509
Cochran-Armitage Trend Test (d)	P=0.200			
Fisher Exact Tests		P=0.181	P=0.102	P=0.181
Tongue: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	9.6%	12.7%
Terminal Rates (c)	0/46 (0%)	0/38 (0%)	0/34 (0%)	1/25 (4%)
Life Table Tests (d)	P=0.004	(e)	P=0.047	P=0.024
Incidental Tumor Tests (d)	P=0.167	(e)	P=0.240	P=0.233
Cochran-Armitage Trend Test (d)	P=0.014			
Fisher Exact Tests		(e)	P=0.059	P=0.059
Tongue: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	0/50 (0%)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	0.0%	2.6%	11.6%	12.7%
Terminal Rates (c)	0/46 (0%)	1/38 (3%)	0/34 (0%)	1/25 (4%)
Life Table Tests (d)	P=0.010	P=0.462	P=0.025	P=0.024
Incidental Tumor Tests (d)	P=0.274	P=0.462	P=0.240	P=0.233
Cochran-Armitage Trend Test (d)	P=0.031			
Fisher Exact Tests		P=0.500	P=0.028	P=0.059
Oral Cavity: Squamous Cell Papilloma				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	2.2%	10.5%	21.4%	16.2%
Terminal Rates (c)	1/46 (2%)	4/38 (11%)	6/34 (18%)	3/25 (12%)
Life Table Tests (d)	P=0.017	P=0.127	P=0.006	P=0.032
Incidental Tumor Tests (d)	P=0.047	P=0.127	P=0.022	P=0.121
Cochran-Armitage Trend Test (d)	P=0.105			
Fisher Exact Tests		P=0.181	P=0.015	P=0.102
Oral Cavity: Squamous Cell Carcinoma				
Overall Rates (a)	0/50 (0%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	0.0%	2.5%	9.6%	15.4%
Terminal Rates (c)	0/46 (0%)	0/38 (0%)	0/34 (0%)	1/25 (4%)
Life Table Tests (d)	P=0.003	P=0.468	P=0.047	P=0.010
Incidental Tumor Tests (d)	P=0.201	P=0.557	P=0.240	P=0.184
Cochran-Armitage Trend Test (d)	P=0.011			
Fisher Exact Tests		P=0.500	P=0.059	P=0.028

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Oral Cavity: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	1/50 (2%)	5/50 (10%)	12/50 (24%)	9/50 (18%)
Adjusted Rates (b)	2.2%	12.8%	28.9%	27.7%
Terminal Rates (c)	1/46 (2%)	4/38 (11%)	6/34 (18%)	4/25 (16%)
Life Table Tests (d)	P<0.001	P=0.068	P<0.001	P=0.001
Incidental Tumor Tests (d)	P=0.039	P=0.081	P=0.007	P=0.029
Cochran-Armitage Trend Test (d)	P=0.010			
Fisher Exact Tests		P=0.102	P<0.001	P=0.008
Liver: Neoplastic Nodule				
Overall Rates (a)	0/50 (0%)	3/49 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.9%	2.9%	0.0%
Terminal Rates (c)	0/46 (0%)	3/38 (8%)	1/34 (3%)	0/25 (0%)
Life Table Tests (d)	P=0.534N	P=0.090	P=0.440	(e)
Incidental Tumor Tests (d)	P=0.534N	P=0.090	P=0.440	(e)
Cochran-Armitage Trend Test (d)	P=0.365N			
Fisher Exact Tests		P=0.117	P=0.500	(e)
Pituitary: Adenoma				
Overall Rates (a)	22/47 (47%)	15/50 (30%)	15/48 (31%)	8/49 (16%)
Adjusted Rates (b)	48.7%	35.3%	38.4%	26.0%
Terminal Rates (c)	20/43 (47%)	11/38 (29%)	11/34 (32%)	5/25 (20%)
Life Table Tests (d)	P=0.101N	P=0.230N	P=0.352N	P=0.102N
Incidental Tumor Tests (d)	P=0.002N	P=0.074N	P=0.080N	P=0.008N
Cochran-Armitage Trend Test (d)	P=0.002N			
Fisher Exact Tests		P=0.067N	P=0.089N	P=0.001N
Thyroid: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	2/50 (4%)	4/50 (8%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	4.3%	10.5%	11.8%	0.0%
Terminal Rates (c)	2/46 (4%)	4/38 (11%)	4/34 (12%)	0/25 (0%)
Life Table Tests (d)	P=0.371N	P=0.253	P=0.209	P=0.380N
Incidental Tumor Tests (d)	P=0.371N	P=0.253	P=0.209	P=0.380N
Cochran-Armitage Trend Test (d)	P=0.167N			
Fisher Exact Tests		P=0.339	P=0.339	P=0.253N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	2.2%	10.5%	11.8%	4.0%
Terminal Rates (c)	1/46 (2%)	4/38 (11%)	4/34 (12%)	1/25 (4%)
Life Table Tests (d)	P=0.445	P=0.127	P=0.101	P=0.620
Incidental Tumor Tests (d)	P=0.445	P=0.127	P=0.101	P=0.620
Cochran-Armitage Trend Test (d)	P=0.466N			
Fisher Exact Tests		P=0.181	P=0.181	P=0.747
Thyroid: C-Cell Carcinoma				
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	6.5%	7.9%	2.5%	6.7%
Terminal Rates (c)	3/46 (7%)	3/38 (8%)	0/34 (0%)	1/25 (4%)
Life Table Tests (d)	P=0.568N	P=0.572	P=0.408N	P=0.625
Incidental Tumor Tests (d)	P=0.376N	P=0.572	P=0.324N	P=0.609N
Cochran-Armitage Trend Test (d)	P=0.351N			
Fisher Exact Tests		P=0.661	P=0.309N	P=0.510N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	7/50 (14%)	5/50 (10%)	3/49 (6%)
Adjusted Rates (b)	8.7%	18.4%	14.0%	10.6%
Terminal Rates (c)	4/46 (9%)	7/38 (18%)	4/34 (12%)	2/25 (8%)
Life Table Tests (d)	P=0.479	P=0.162	P=0.325	P=0.513
Incidental Tumor Tests (d)	P=0.519N	P=0.162	P=0.380	P=0.639
Cochran-Armitage Trend Test (d)	P=0.310N			
Fisher Exact Tests		P=0.262	P=0.500	P=0.511N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Mammary Gland: Fibroadenoma				
Overall Rates (a)	10/50 (20%)	14/50 (28%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	20.8%	33.0%	28.4%	13.8%
Terminal Rates (c)	8/46 (17%)	10/38 (26%)	9/34 (26%)	2/25 (8%)
Life Table Tests (d)	P=0.277N	P=0.127	P=0.317	P=0.363N
Incidental Tumor Tests (d)	P=0.043N	P=0.297	P=0.444	P=0.074N
Cochran-Armitage Trend Test (d)	P=0.029N			
Fisher Exact Tests		P=0.241	P=0.598	P=0.074N
Clitoral Gland: Carcinoma				
Overall Rates (a)	2/50 (4%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	4.3%	0.0%	0.0%	8.8%
Terminal Rates (c)	2/46 (4%)	0/38 (0%)	0/34 (0%)	0/25 (0%)
Life Table Tests (d)	P=0.142	P=0.281N	P=0.307N	P=0.304
Incidental Tumor Tests (d)	P=0.401	P=0.281N	P=0.307N	P=0.579N
Cochran-Armitage Trend Test (d)	P=0.245			
Fisher Exact Tests		P=0.247N	P=0.247N	P=0.500
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	7/50 (14%) (f)	7/50 (14%)	7/49 (14%)	14/50 (28%)
Adjusted Rates (b)	14.8%	17.4%	17.6%	44.5%
Terminal Rates (c)	6/46 (13%)	5/38 (13%)	4/34 (12%)	9/25 (36%)
Life Table Tests (d)	P=0.001	P=0.468	P=0.420	P=0.003
Incidental Tumor Tests (d)	P=0.049	P=0.545	P=0.598N	P=0.049
Cochran-Armitage Trend Test (d)	P=0.032			
Fisher Exact Tests		P=0.613	P=0.597	P=0.070
Uterus: Carcinoma or Adenocarcinoma				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	5.3%	8.4%	6.7%
Terminal Rates (c)	0/46 (0%)	2/38 (5%)	2/34 (6%)	1/25 (4%)
Life Table Tests (d)	P=0.099	P=0.197	P=0.078	P=0.148
Incidental Tumor Tests (d)	P=0.244	P=0.197	P=0.121	P=0.293
Cochran-Armitage Trend Test (d)	P=0.237			
Fisher Exact Tests		P=0.247	P=0.117	P=0.247
Uterus: Adenoma, Carcinoma, or Adenocarcinoma				
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	7.9%	8.4%	6.7%
Terminal Rates (c)	0/46 (0%)	3/38 (8%)	2/34 (6%)	1/25 (4%)
Life Table Tests (d)	P=0.137	P=0.090	P=0.078	P=0.148
Incidental Tumor Tests (d)	P=0.295	P=0.090	P=0.121	P=0.293
Cochran-Armitage Trend Test (d)	P=0.312			
Fisher Exact Tests		P=0.121	P=0.117	P=0.247
Zymbal Gland: Carcinoma				
Overall Rates (a)	0/45 (0%)	5/40 (10%)	5/44 (11%)	14/46 (30%)
Adjusted Rates (b)	0.0%	13.3%	14.4%	42.0%
Terminal Rates (c)	0/41 (0%)	3/33 (9%)	3/29 (10%)	8/25 (32%)
Life Table Tests (d)	P<0.001	P=0.022	P=0.018	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.036	P=0.067	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.020	P=0.026	P<0.001
Zymbal Gland: Adenoma or Carcinoma				
Overall Rates (a)	0/45 (0%)	5/40 (13%)	6/44 (14%)	15/46 (33%)
Adjusted Rates (b)	0.0%	13.3%	16.2%	45.4%
Terminal Rates (c)	0/41 (0%)	3/33 (9%)	4/29 (14%)	9/25 (36%)
Life Table Tests (d)	P<0.001	P=0.022	P=0.010	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.036	P=0.021	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.020	P=0.012	P<0.001

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

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

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Skin: Squamous Cell Carcinoma				
Overall Rates (a)	0/49 (0%)	0/48 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	11.1%	23.3%
Terminal Rates (c)	0/28 (0%)	0/23 (0%)	2/18 (11%)	1/7 (14%)
Life Table Tests (d)	P=0.001	(e)	P=0.147	P=0.024
Incidental Tumor Tests (d)	P=0.008	(e)	P=0.147	P=0.128
Cochran-Armitage Trend Test (d)	P=0.028			
Fisher Exact Tests		(e)	P=0.253	P=0.121
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	6/49 (12%)	4/48 (8%)	9/50 (18%)	3/49 (6%)
Adjusted Rates (b)	16.3%	11.1%	26.7%	11.5%
Terminal Rates (c)	1/28 (4%)	0/23 (0%)	0/18 (0%)	0/7 (0%)
Life Table Tests (d)	P=0.526	P=0.446N	P=0.180	P=0.545N
Incidental Tumor Tests (d)	P=0.017N	P=0.241N	P=0.489N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.290N			
Fisher Exact Tests		P=0.383N	P=0.303	P=0.243N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	6/49 (12%)	5/48 (10%)	9/50 (18%)	3/49 (6%)
Adjusted Rates (b)	16.3%	14.9%	26.7%	11.5%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	0/18 (0%)	0/7 (0%)
Life Table Tests (d)	P=0.535	P=0.580N	P=0.180	P=0.545N
Incidental Tumor Tests (d)	P=0.018N	P=0.384N	P=0.489N	P=0.043N
Cochran-Armitage Trend Test (d)	P=0.256N			
Fisher Exact Tests		P=0.515N	P=0.303	P=0.243N
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	6/49 (12%)	6/48 (13%)	8/50 (16%)	12/49 (24%)
Adjusted Rates (b)	18.9%	21.1%	29.3%	41.5%
Terminal Rates (c)	4/28 (14%)	3/23 (13%)	2/18 (11%)	0/7 (0%)
Life Table Tests (d)	P<0.001	P=0.499	P=0.188	P=0.005
Incidental Tumor Tests (d)	P=0.179	P=0.609	P=0.486	P=0.326
Cochran-Armitage Trend Test (d)	P=0.047			
Fisher Exact Tests		P=0.606	P=0.403	P=0.096
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	5/49 (10%)	11/48 (23%)	12/50 (24%)	14/49 (29%)
Adjusted Rates (b)	15.6%	36.3%	41.9%	58.8%
Terminal Rates (c)	3/28 (11%)	6/23 (26%)	5/18 (28%)	2/7 (29%)
Life Table Tests (d)	P<0.001	P=0.052	P=0.017	P<0.001
Incidental Tumor Tests (d)	P=0.046	P=0.083	P=0.083	P=0.073
Cochran-Armitage Trend Test (d)	P=0.028			
Fisher Exact Tests		P=0.078	P=0.059	P=0.020
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	10/49 (20%)	16/48 (33%)	19/50 (38%)	21/49 (43%)
Adjusted Rates (b)	29.8%	49.1%	60.0%	71.1%
Terminal Rates (c)	6/28 (21%)	8/23 (35%)	7/18 (39%)	2/7 (29%)
Life Table Tests (d)	P<0.001	P=0.069	P=0.007	P<0.001
Incidental Tumor Tests (d)	P=0.056	P=0.124	P=0.070	P=0.094
Cochran-Armitage Trend Test (d)	P=0.015			
Fisher Exact Tests		P=0.113	P=0.044	P=0.014
Hematopoietic System: Malignant Lymphoma, Histiocytic Type				
Overall Rates (a)	0/49 (0%)	0/48 (0%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	13.0%	18.8%
Terminal Rates (c)	0/28 (0%)	0/23 (0%)	2/18 (11%)	1/7 (14%)
Life Table Tests (d)	P=0.005	(e)	P=0.077	P=0.051
Incidental Tumor Tests (d)	P=0.017	(e)	P=0.116	P=0.128
Cochran-Armitage Trend Test (d)	P=0.035			
Fisher Exact Tests		(e)	P=0.125	P=0.121

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	4/49 (8%)	9/48 (19%)	9/50 (18%)	15/49 (31%)
Adjusted Rates (b)	12.4%	31.3%	42.2%	69.3%
Terminal Rates (c)	2/28 (7%)	5/23 (22%)	7/18 (39%)	3/7 (43%)
Life Table Tests (d)	P<0.001	P=0.075	P=0.030	P<0.001
Incidental Tumor Tests (d)	P=0.003	P=0.116	P=0.072	P=0.022
Cochran-Armitage Trend Test (d)	P=0.005			
Fisher Exact Tests		P=0.109	P=0.125	P=0.005
Hematopoietic System: Lymphoma or Leukemia				
Overall Rates (a)	4/49 (8%)	10/48 (21%)	10/50 (20%)	15/49 (31%)
Adjusted Rates (b)	12.4%	33.1%	44.0%	69.3%
Terminal Rates (c)	2/28 (7%)	5/23 (22%)	7/18 (39%)	3/7 (43%)
Life Table Tests (d)	P<0.001	P=0.048	P=0.018	P<0.001
Incidental Tumor Tests (d)	P=0.006	P=0.080	P=0.052	P=0.022
Cochran-Armitage Trend Test (d)	P=0.006			
Fisher Exact Tests		P=0.068	P=0.080	P=0.005
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	3/49 (6%)	2/48 (4%)	3/50 (6%)	4/49 (8%)
Adjusted Rates (b)	8.9%	5.9%	7.9%	17.9%
Terminal Rates (c)	1/28 (4%)	0/23 (0%)	0/18 (0%)	0/7 (0%)
Life Table Tests (d)	P=0.163	P=0.552N	P=0.582	P=0.197
Incidental Tumor Tests (d)	P=0.467N	P=0.456N	P=0.478N	P=0.514N
Cochran-Armitage Trend Test (d)	P=0.348			
Fisher Exact Tests		P=0.510N	P=0.651N	P=0.500
Liver: Hepatocellular Adenoma				
Overall Rates (a)	7/49 (14%)	11/48 (23%)	6/50 (12%)	3/47 (6%)
Adjusted Rates (b)	25.0%	40.4%	25.4%	14.5%
Terminal Rates (c)	7/28 (25%)	8/23 (35%)	3/18 (17%)	0/7 (0%)
Life Table Tests (d)	P=0.519	P=0.108	P=0.438	P=0.518
Incidental Tumor Tests (d)	P=0.221N	P=0.131	P=0.583	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.064N			
Fisher Exact Tests		P=0.203	P=0.484N	P=0.176N
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	9/49 (18%)	8/48 (17%)	17/50 (34%)	8/47 (17%)
Adjusted Rates (b)	22.0%	27.8%	49.4%	46.7%
Terminal Rates (c)	1/28 (4%)	4/23 (17%)	3/18 (17%)	2/7 (29%)
Life Table Tests (d)	P=0.072	P=0.589	P=0.028	P=0.293
Incidental Tumor Tests (d)	P=0.234N	P=0.392N	P=0.231	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.488			
Fisher Exact Tests		P=0.519N	P=0.061	P=0.538N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	15/49 (31%)	17/48 (35%)	22/50 (44%)	11/47 (23%)
Adjusted Rates (b)	39.3%	54.9%	62.7%	54.8%
Terminal Rates (c)	7/28 (25%)	10/23 (43%)	6/18 (33%)	2/7 (29%)
Life Table Tests (d)	P=0.076	P=0.256	P=0.029	P=0.225
Incidental Tumor Tests (d)	P=0.136N	P=0.423	P=0.238	P=0.207N
Cochran-Armitage Trend Test (d)	P=0.248N			
Fisher Exact Tests		P=0.387	P=0.121	P=0.287N
Stomach: Squamous Cell Papilloma				
Overall Rates (a)	2/45 (4%)	1/42 (2%)	2/44 (5%)	5/38 (13%)
Adjusted Rates (b)	6.8%	4.3%	8.7%	38.5%
Terminal Rates (c)	1/28 (4%)	1/23 (4%)	1/18 (6%)	2/7 (29%)
Life Table Tests (d)	P=0.003	P=0.567N	P=0.556	P=0.014
Incidental Tumor Tests (d)	P=0.048	P=0.546N	P=0.685	P=0.161
Cochran-Armitage Trend Test (d)	P=0.050			
Fisher Exact Tests		P=0.526N	P=0.683	P=0.153

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Stomach: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	2/45 (4%)	2/42 (5%)	3/44 (7%)	5/38 (13%)
Adjusted Rates (b)	6.8%	8.7%	13.3%	38.5%
Terminal Rates (c)	1/28 (4%)	2/23 (9%)	1/18 (6%)	2/7 (29%)
Life Table Tests (d)	P=0.004	P=0.623	P=0.335	P=0.014
Incidental Tumor Tests (d)	P=0.074	P=0.640	P=0.521	P=0.161
Cochran-Armitage Trend Test (d)	P=0.075			
Fisher Exact Tests		P=0.665	P=0.489	P=0.153
Adrenal: Pheochromocytoma				
Overall Rates (a)	1/47 (2%)	1/48 (2%)	7/49 (14%)	1/46 (2%)
Adjusted Rates (b)	2.9%	4.3%	30.0%	4.3%
Terminal Rates (c)	0/27 (0%)	1/23 (4%)	3/18 (17%)	0/6 (0%)
Life Table Tests (d)	P=0.096	P=0.725	P=0.010	P=0.632
Incidental Tumor Tests (d)	P=0.540	P=0.757N	P=0.045	P=0.529N
Cochran-Armitage Trend Test (d)	P=0.444			
Fisher Exact Tests		P=0.747N	P=0.034	P=0.747
Thyroid: Follicular Cell Adenoma				
Overall Rates (a)	3/47 (6%)	0/47 (0%)	1/49 (2%)	1/44 (2%)
Adjusted Rates (b)	10.7%	0.0%	4.3%	14.3%
Terminal Rates (c)	3/28 (11%)	0/22 (0%)	0/18 (0%)	1/7 (14%)
Life Table Tests (d)	P=0.632	P=0.165N	P=0.465N	P=0.653
Incidental Tumor Tests (d)	P=0.518N	P=0.165N	P=0.371N	P=0.653
Cochran-Armitage Trend Test (d)	P=0.311N			
Fisher Exact Tests		P=0.121N	P=0.293N	P=0.334N
Preputial Gland: Squamous Cell Carcinoma				
Overall Rates (a)	0/21 (0%)	3/28 (11%)	18/29 (62%)	28/35 (80%)
Adjusted Rates (b)	0.0%	13.6%	80.8%	91.2%
Terminal Rates (c)	0/13 (0%)	3/22 (14%)	14/18 (78%)	4/6 (67%)
Life Table Tests (d)	P<0.001	P=0.225	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.225	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.178	P<0.001	P<0.001
Preputial Gland: All Carcinoma				
Overall Rates (a)	0/21 (0%)	5/28 (18%)	19/29 (66%)	31/35 (89%)
Adjusted Rates (b)	0.0%	21.7%	81.6%	96.1%
Terminal Rates (c)	0/13 (0%)	5/22 (22%)	14/18 (78%)	5/6 (83%)
Life Table Tests (d)	P<0.001	P=0.091	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.091	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.052	P<0.001	P<0.001
Harderian Gland: Adenoma				
Overall Rates (a)	0/49 (0%)	9/46 (20%)	13/49 (27%)	11/48 (23%)
Adjusted Rates (b)	0.0%	33.2%	51.7%	56.2%
Terminal Rates (c)	0/28 (0%)	6/22 (27%)	8/18 (44%)	2/7 (29%)
Life Table Tests (d)	P<0.001	P=0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.001	P=0.001	P<0.001	P=0.003
Cochran-Armitage Trend Test (d)	P=0.004			
Fisher Exact Tests		P<0.001	P<0.001	P<0.001
Harderian Gland: Carcinoma				
Overall Rates (a)	1/49 (2%)	2/46 (4%)	0/49 (0%)	3/48 (6%)
Adjusted Rates (b)	3.6%	8.4%	0.0%	11.7%
Terminal Rates (c)	1/28 (4%)	1/22 (5%)	0/18 (0%)	0/7 (0%)
Life Table Tests (d)	P=0.064	P=0.423	P=0.588N	P=0.128
Incidental Tumor Tests (d)	P=0.309	P=0.467	P=0.588N	P=0.397
Cochran-Armitage Trend Test (d)	P=0.242			
Fisher Exact Tests		P=0.476	P=0.500N	P=0.301

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Harderian Gland: Adenoma or Carcinoma				
Overall Rates (a)	1/49 (2%)	10/46 (22%)	13/49 (27%)	14/48 (29%)
Adjusted Rates (b)	3.6%	35.8%	51.7%	61.3%
Terminal Rates (c)	1/28 (4%)	6/22 (27%)	8/18 (44%)	2/7 (29%)
Life Table Tests (d)	P<0.001	P=0.002	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.003	P<0.001	P=0.002
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Tests		P=0.003	P<0.001	P<0.001
Zymbal Gland: Squamous Cell Carcinoma				
Overall Rates (a)	0/43 (0%)	1/34 (3%)	4/40 (10%)	21/39 (54%)
Adjusted Rates (b)	0.0%	2.9%	28.6%	87.6%
Terminal Rates (c)	0/25 (0%)	0/15 (0%)	4/14 (29%)	5/7 (71%)
Life Table Tests (d)	P<0.001	P=0.489	P=0.012	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.500	P=0.012	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.442	P=0.050	P<0.001

(a) Number of tumor-bearing animals/number of animals examined at the site. Mice dying before week 4 are not included in these analyses.
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups.

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	1/49 (2%)	4/45 (9%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	2.9%	10.3%	11.0%	3.0%
Terminal Rates (c)	0/30 (0%)	0/26 (0%)	1/24 (4%)	0/18 (0%)
Life Table Tests (d)	P=0.572N	P=0.157	P=0.231	P=0.673
Incidental Tumor Tests (d)	P=0.242N	P=0.183	P=0.404	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.418N			
Fisher Exact Tests		P=0.155	P=0.316	P=0.753
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	4/49 (8%)	2/42 (5%)	5/50 (10%)	9/49 (18%)
Adjusted Rates (b)	13.3%	7.2%	15.7%	44.0%
Terminal Rates (c)	4/30 (13%)	1/24 (4%)	2/24 (8%)	7/18 (39%)
Life Table Tests (d)	P=0.003	P=0.437N	P=0.398	P=0.011
Incidental Tumor Tests (d)	P=0.010	P=0.435N	P=0.514	P=0.020
Cochran-Armitage Trend Test (d)	P=0.035			
Fisher Exact Tests		P=0.415N	P=0.513	P=0.116
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	0/49 (0%)	3/42 (7%)	6/50 (12%)	6/49 (12%)
Adjusted Rates (b)	0.0%	12.5%	22.8%	27.0%
Terminal Rates (c)	0/30 (0%)	3/24 (13%)	5/24 (21%)	4/18 (22%)
Life Table Tests (d)	P=0.002	P=0.084	P=0.010	P=0.004
Incidental Tumor Tests (d)	P=0.006	P=0.084	P=0.013	P=0.009
Cochran-Armitage Trend Test (d)	P=0.021			
Fisher Exact Tests		P=0.094	P=0.014	P=0.013
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	4/49 (8%)	5/42 (12%)	10/50 (20%)	13/49 (27%)
Adjusted Rates (b)	13.3%	19.3%	32.7%	57.1%
Terminal Rates (c)	4/30 (13%)	4/24 (17%)	6/24 (25%)	9/18 (50%)
Life Table Tests (d)	P<0.001	P=0.366	P=0.039	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.368	P=0.071	P=0.002
Cochran-Armitage Trend Test (d)	P=0.007			
Fisher Exact Tests		P=0.402	P=0.080	P=0.015
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type				
Overall Rates (a)	2/49 (4%)	2/45 (4%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	6.7%	4.8%	7.0%	11.1%
Terminal Rates (c)	2/30 (7%)	0/26 (0%)	1/24 (4%)	0/18 (0%)
Life Table Tests (d)	P=0.149	P=0.658	P=0.625	P=0.234
Incidental Tumor Tests (d)	P=0.307	P=0.682	P=0.675	P=0.319
Cochran-Armitage Trend Test (d)	P=0.233			
Fisher Exact Tests		P=0.659	P=0.684N	P=0.339
Hematopoietic System: Malignant Lymphoma, Histiocytic Type				
Overall Rates (a)	0/49 (0%)	3/45 (7%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	0.0%	10.2%	6.4%	2.6%
Terminal Rates (c)	0/30 (0%)	1/26 (4%)	0/24 (0%)	0/18 (0%)
Life Table Tests (d)	P=0.426	P=0.097	P=0.136	P=0.480
Incidental Tumor Tests (d)	P=0.455N	P=0.111	P=0.230	P=0.701
Cochran-Armitage Trend Test (d)	P=0.538			
Fisher Exact Tests		P=0.106	P=0.125	P=0.500
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	15/49 (31%)	24/45 (53%)	24/50 (48%)	20/49 (41%)
Adjusted Rates (b)	41.7%	68.0%	62.5%	53.6%
Terminal Rates (c)	10/30 (33%)	15/26 (58%)	11/24 (46%)	5/18 (28%)
Life Table Tests (d)	P=0.031	P=0.021	P=0.025	P=0.037
Incidental Tumor Tests (d)	P=0.446	P=0.028	P=0.109	P=0.357
Cochran-Armitage Trend Test (d)	P=0.335			
Fisher Exact Tests		P=0.021	P=0.059	P=0.200

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Hematopoietic System: Lymphoma or Leukemia				
Overall Rates (a)	15/49 (31%)	25/45 (56%)	26/50 (52%)	22/49 (45%)
Adjusted Rates (b)	41.7%	68.7%	64.6%	56.2%
Terminal Rates (c)	10/30 (33%)	15/26 (58%)	11/24 (46%)	5/18 (28%)
Life Table Tests (d)	P=0.014	P=0.014	P=0.012	P=0.017
Incidental Tumor Tests (d)	P=0.309	P=0.014	P=0.061	P=0.272
Cochran-Armitage Trend Test (d)	P=0.204			
Fisher Exact Tests		P=0.012	P=0.025	P=0.105
Liver: Hepatocellular Adenoma				
Overall Rates (a)	1/49 (2%)	8/44 (18%)	5/50 (10%)	4/49 (8%)
Adjusted Rates (b)	3.3%	30.8%	15.6%	17.4%
Terminal Rates (c)	1/30 (3%)	8/26 (31%)	1/24 (4%)	2/18 (11%)
Life Table Tests (d)	P=0.156	P=0.008	P=0.079	P=0.077
Incidental Tumor Tests (d)	P=0.289	P=0.008	P=0.168	P=0.124
Cochran-Armitage Trend Test (d)	P=0.426			
Fisher Exact Tests		P=0.010	P=0.107	P=0.181
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	3/49 (6%)	4/44 (9%)	8/50 (16%)	4/49 (8%)
Adjusted Rates (b)	9.1%	11.9%	28.0%	17.0%
Terminal Rates (c)	2/30 (7%)	1/26 (4%)	5/24 (21%)	1/18 (6%)
Life Table Tests (d)	P=0.169	P=0.440	P=0.058	P=0.278
Incidental Tumor Tests (d)	P=0.401	P=0.498	P=0.101	P=0.471
Cochran-Armitage Trend Test (d)	P=0.413			
Fisher Exact Tests		P=0.439	P=0.106	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	4/49 (8%)	12/44 (27%)	13/50 (26%)	7/49 (14%)
Adjusted Rates (b)	12.3%	40.1%	39.9%	27.5%
Terminal Rates (c)	3/30 (10%)	9/26 (35%)	6/24 (25%)	2/18 (11%)
Life Table Tests (d)	P=0.103	P=0.014	P=0.008	P=0.086
Incidental Tumor Tests (d)	P=0.339	P=0.017	P=0.026	P=0.209
Cochran-Armitage Trend Test (d)	P=0.438			
Fisher Exact Tests		P=0.015	P=0.017	P=0.262
Stomach: Squamous Cell Papilloma				
Overall Rates (a)	1/42 (2%)	3/40 (7%)	6/45 (13%)	5/42 (12%)
Adjusted Rates (b)	2.3%	8.6%	23.7%	25.1%
Terminal Rates (c)	0/29 (0%)	1/26 (4%)	5/24 (21%)	4/18 (22%)
Life Table Tests (d)	P=0.022	P=0.288	P=0.038	P=0.040
Incidental Tumor Tests (d)	P=0.071	P=0.134	P=0.059	P=0.079
Cochran-Armitage Trend Test (d)	P=0.083			
Fisher Exact Tests		P=0.289	P=0.066	P=0.101
Pituitary: Adenoma				
Overall Rates (a)	13/45 (29%)	5/35 (14%)	6/45 (13%)	4/35 (11%)
Adjusted Rates (b)	44.5%	22.8%	23.6%	23.2%
Terminal Rates (c)	12/28 (43%)	4/20 (20%)	5/24 (21%)	3/15 (20%)
Life Table Tests (d)	P=0.130N	P=0.119N	P=0.109N	P=0.184N
Incidental Tumor Tests (d)	P=0.081N	P=0.117N	P=0.076N	P=0.133N
Cochran-Armitage Trend Test (d)	P=0.038N			
Fisher Exact Tests		P=0.099N	P=0.060N	P=0.051N
Adrenal: Pheochromocytoma				
Overall Rates (a)	6/49 (12%)	1/44 (2%)	1/50 (2%)	1/48 (2%)
Adjusted Rates (b)	20.0%	3.8%	4.2%	5.9%
Terminal Rates (c)	6/30 (20%)	1/26 (4%)	1/24 (4%)	1/17 (6%)
Life Table Tests (d)	P=0.097N	P=0.080N	P=0.097N	P=0.192N
Incidental Tumor Tests (d)	P=0.097N	P=0.080N	P=0.097N	P=0.192N
Cochran-Armitage Trend Test (d)	P=0.036N			
Fisher Exact Tests		P=0.074N	P=0.053N	P=0.059N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	8/49 (16%)	1/44 (2%)	1/50 (2%)	1/48 (2%)
Adjusted Rates (b)	23.9%	3.8%	4.2%	5.9%
Terminal Rates (c)	6/30 (20%)	1/26 (4%)	1/24 (4%)	1/17 (6%)
Life Table Tests (d)	P=0.030N	P=0.030N	P=0.035N	P=0.085N
Incidental Tumor Tests (d)	P=0.018N	P=0.033N	P=0.025N	P=0.046N
Cochran-Armitage Trend Test (d)	P=0.009N			
Fisher Exact Tests		P=0.023N	P=0.014N	P=0.017N
Adrenal Capsule: Adenoma				
Overall Rates (a)	0/49 (0%)	0/44 (0%)	3/50 (6%)	0/48 (0%)
Adjusted Rates (b)	0.0%	0.0%	12.5%	0.0%
Terminal Rates (c)	0/30 (0%)	0/26 (0%)	3/24 (13%)	0/17 (0%)
Life Table Tests (d)	P=0.399	(e)	P=0.084	(e)
Incidental Tumor Tests (d)	P=0.399	(e)	P=0.084	(e)
Cochran-Armitage Trend Test (d)	P=0.543			
Fisher Exact Tests		(e)	P=0.125	(e)
Thyroid: Follicular Cell Adenoma				
Overall Rates (a)	3/48 (6%)	1/42 (2%)	1/48 (2%)	1/46 (2%)
Adjusted Rates (b)	10.0%	3.8%	4.2%	5.6%
Terminal Rates (c)	3/30 (10%)	1/26 (4%)	1/24 (4%)	1/18 (6%)
Life Table Tests (d)	P=0.389N	P=0.356N	P=0.387N	P=0.500N
Incidental Tumor Tests (d)	P=0.389N	P=0.356N	P=0.387N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.243N			
Fisher Exact Tests		P=0.360N	P=0.308N	P=0.325N
Mammary Gland: Carcinoma				
Overall Rates (a)	0/49 (0%)	2/45 (4%)	5/50 (10%)	10/49 (20%)
Adjusted Rates (b)	0.0%	6.9%	15.9%	33.2%
Terminal Rates (c)	0/30 (0%)	0/26 (0%)	2/24 (8%)	3/18 (17%)
Life Table Tests (d)	P<0.001	P=0.202	P=0.026	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.233	P=0.047	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Tests		P=0.226	P=0.030	P<0.001
Mammary Gland: Carcinosarcoma				
Overall Rates (a)	0/49 (0%)	0/45 (0%)	1/50 (2%)	4/49 (8%)
Adjusted Rates (b)	0.0%	0.0%	2.7%	20.6%
Terminal Rates (c)	0/30 (0%)	0/26 (0%)	0/24 (0%)	3/18 (17%)
Life Table Tests (d)	P=0.001	(e)	P=0.495	P=0.017
Incidental Tumor Tests (d)	P=0.003	(e)	P=0.588	P=0.030
Cochran-Armitage Trend Test (d)	P=0.006			
Fisher Exact Tests		(e)	P=0.505	P=0.059
Ovary: Granulosa Cell Tumor				
Overall Rates (a)	1/47 (2%)	1/44 (2%)	6/49 (12%)	7/48 (15%)
Adjusted Rates (b)	3.3%	3.8%	19.9%	28.9%
Terminal Rates (c)	1/30 (3%)	1/26 (4%)	3/24 (13%)	4/18 (22%)
Life Table Tests (d)	P<0.001	P=0.730	P=0.040	P=0.008
Incidental Tumor Tests (d)	P=0.005	P=0.730	P=0.077	P=0.020
Cochran-Armitage Trend Test (d)	P=0.008			
Fisher Exact Tests		P=0.736	P=0.062	P=0.032
Ovary: Granulosa Cell Tumor or Carcinoma				
Overall Rates (a)	1/47 (2%)	1/44 (2%)	6/49 (12%)	8/48 (17%)
Adjusted Rates (b)	3.3%	3.8%	19.9%	31.6%
Terminal Rates (c)	1/30 (3%)	1/26 (4%)	3/24 (13%)	4/18 (22%)
Life Table Tests (d)	P<0.001	P=0.730	P=0.040	P=0.004
Incidental Tumor Tests (d)	P=0.002	P=0.730	P=0.077	P=0.012
Cochran-Armitage Trend Test (d)	P=0.003			
Fisher Exact Tests		P=0.736	P=0.062	P=0.017

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg	100 mg/kg
Ovary: Luteoma				
Overall Rates (a)	0/47 (0%)	2/44 (5%)	3/49 (6%)	2/48 (4%)
Adjusted Rates (b)	0.0%	7.7%	11.6%	11.1%
Terminal Rates (c)	0/30 (0%)	2/26 (8%)	2/24 (8%)	2/18 (11%)
Life Table Tests (d)	P=0.102	P=0.207	P=0.088	P=0.134
Incidental Tumor Tests (d)	P=0.125	P=0.207	P=0.119	P=0.134
Cochran-Armitage Trend Test (d)	P=0.253			
Fisher Exact Tests		P=0.231	P=0.129	P=0.253
Ovary: Tubular Adenoma				
Overall Rates (a)	0/47 (0%)	0/44 (0%)	3/49 (6%)	3/48 (6%)
Adjusted Rates (b)	0.0%	0.0%	11.4%	15.8%
Terminal Rates (c)	0/30 (0%)	0/26 (0%)	2/24 (8%)	2/18 (11%)
Life Table Tests (d)	P=0.008	(e)	P=0.090	P=0.047
Incidental Tumor Tests (d)	P=0.016	(e)	P=0.119	P=0.077
Cochran-Armitage Trend Test (d)	P=0.038			
Fisher Exact Tests		(e)	P=0.129	P=0.125
Ovary: Mixed Tumor, Benign				
Overall Rates (a)	0/47 (0%)	1/44 (2%)	12/49 (24%)	7/48 (15%)
Adjusted Rates (b)	0.0%	3.8%	42.3%	32.9%
Terminal Rates (c)	0/30 (0%)	1/26 (4%)	9/24 (38%)	5/18 (28%)
Life Table Tests (d)	P<0.001	P=0.471	P<0.001	P=0.001
Incidental Tumor Tests (d)	P<0.001	P=0.471	P<0.001	P=0.002
Cochran-Armitage Trend Test (d)	P=0.004			
Fisher Exact Tests		P=0.484	P<0.001	P=0.007
Harderian Gland: Adenoma				
Overall Rates (a)	5/48 (10%)	6/44 (14%)	10/50 (20%)	6/47 (13%)
Adjusted Rates (b)	16.7%	24.0%	27.4%	27.1%
Terminal Rates (c)	5/30 (17%)	6/25 (24%)	2/24 (8%)	4/18 (22%)
Life Table Tests (d)	P=0.133	P=0.369	P=0.090	P=0.204
Incidental Tumor Tests (d)	P=0.311	P=0.369	P=0.209	P=0.281
Cochran-Armitage Trend Test (d)	P=0.413			
Fisher Exact Tests		P=0.438	P=0.150	P=0.485
Harderian Gland: Carcinoma				
Overall Rates (a)	0/48 (0%)	0/44 (0%)	0/50 (0%)	4/47 (9%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	17.8%
Terminal Rates (c)	0/30 (0%)	0/25 (0%)	0/24 (0%)	1/18 (6%)
Life Table Tests (d)	P<0.001	(e)	(e)	P=0.020
Incidental Tumor Tests (d)	P=0.003	(e)	(e)	P=0.060
Cochran-Armitage Trend Test (d)	P=0.003			
Fisher Exact Tests		(e)	(e)	P=0.056
Harderian Gland: Adenoma or Carcinoma				
Overall Rates (a)	5/48 (10%)	6/44 (14%)	10/50 (20%)	10/47 (21%)
Adjusted Rates (b)	16.7%	24.0%	27.4%	41.1%
Terminal Rates (c)	5/30 (17%)	6/25 (24%)	2/24 (8%)	5/18 (28%)
Life Table Tests (d)	P=0.009	P=0.369	P=0.090	P=0.017
Incidental Tumor Tests (d)	P=0.046	P=0.369	P=0.209	P=0.049
Cochran-Armitage Trend Test (d)	P=0.081			
Fisher Exact Tests		P=0.438	P=0.150	P=0.121
Zymbal Gland: Squamous Cell Carcinoma				
Overall Rates (a)	0/43 (0%)	0/32 (0%)	1/37 (3%)	3/31 (10%)
Adjusted Rates (b)	0.0%	0.0%	4.8%	18.8%
Terminal Rates (c)	0/27 (0%)	0/18 (0%)	1/21 (5%)	3/16 (19%)
Life Table Tests (d)	P=0.007	(e)	P=0.450	P=0.045
Incidental Tumor Tests (d)	P=0.007	(e)	P=0.450	P=0.045
Cochran-Armitage Trend Test (d)	P=0.011			
Fisher Exact Tests		(e)	P=0.462	P=0.069

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZENE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site. Mice dying before week 4 are not included in these analyses.
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups.

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/50	1/50	1/50
o-Dichlorobenzene	0/50	0/50	0/50
TOTAL	0/100 (0.0%)	1/100 (1.0%)	1/100 (1.0%)
Overall Historical Incidence			
TOTAL	12/1,146 (1.0%)	9/1,146 (0.8%)	21/1,146 (1.8%)
SD (b)	1.69%	1.44%	2.62%
Range (c)			
High	3/50	3/50	5/50
Low	0/52	0/52	0/52

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c)Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM FIBROUS TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	5/50	2/50	7/50
o-Dichlorobenzene	1/50	0/50	1/50
TOTAL	6/100 (6.0%)	2/100 (2.0%)	8/100 (8.0%)
Overall Historical Incidence			
TOTAL	67/1,146 (5.8%)	13/1,146 (1.1%)	77/1,146 (6.7%)
SD (b)	3.12%	2.32%	3.98%
Range (c)			
High	6/50	5/50	7/50
Low	0/50	0/52	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	All Adenoma	All Malignant	Adenoma, Carcinoma, or Adenocarcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	10/50	2/50	12/50
o-Dichlorobenzene	14/49	1/49	15/49
TOTAL	24/99 (24.2%)	3/99 (3.0%)	27/99 (27.3%)
Overall Historical Incidence			
TOTAL	270/1,106 (24.4%)	23/1,106 (2.1%)	293/1,106 (26.5%)
SD (b)	10.87%	2.86%	10.16%
Range (c)			
High	23/48	5/47	23/48
Low	3/47	0/52	6/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks. Includes pituitary and anterior pituitary tumors.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF THYROID GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	C-Cell Adenoma	C-Cell Carcinoma	C-Cell Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/50	6/50	6/50
o-Dichlorobenzene	0/50	2/50	2/50
TOTAL	0/100 (0.0%)	8/100 (8.0%)	8/100 (8.0%)
Overall Historical Incidence			
TOTAL	91/1,109 (8.2%)	48/1,109 (4.3%)	137/1,109 (12.4%)
SD (b)	6.06%	3.46%	6.37%
Range (c)			
High	10/47	6/50	12/49
Low	0/50	0/50	2/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF ORAL CAVITY TUMORS IN F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Battelle Columbus Laboratories				
MALE: No tumors observed in 100 animals.				
FEMALE				
Chlorobenzene	50	0		
o-Dichlorobenzene	50	1	Tongue	Squamous cell papilloma
Overall Historical Incidence				
MALE				
	1,146	1	Oral cavity	Squamous cell papilloma
	1,146	1	Soft palate	Squamous cell carcinoma
FEMALE				
	1,147	2	Tongue	Squamous cell papilloma
		1	Tongue	Squamous cell carcinoma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F6. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	All Adenomas	All Malignant	Adenoma, Carcinoma, or Adenocarcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	23/46	0/46	23/46
o-Dichlorobenzene	13/46	2/46	15/46
TOTAL	36/92 (39.1%)	2/92 (2.2%)	38/92 (41.3%)
Overall Historical Incidence			
TOTAL	410/1,092 (37.5%)	41/1,092 (3.8%)	451/1,092 (41.3%)
SD (b)	10.22%	3.56%	9.28%
Range (c)			
High	28/50	6/46	30/50
Low	8/46	0/49	13/48

(a) Data as of March 16, 1983, for studies of at least 104 weeks. Includes tumors of the pituitary and anterior pituitary gland.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F7. HISTORICAL INCIDENCE OF UTERINE STROMAL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Endometrial Stromal Polyp	Endometrial Stromal Sarcoma
Historical Incidence at Battelle Columbus Laboratories		
Chlorobenzene	16/50	0/50
o-Dichlorobenzene	6/48	0/48
TOTAL	22/98 (22.4%)	0/98 (0.0%)
Overall Historical Incidence		
TOTAL	248/1,125 (22.0%)	23/1,125 (2.0%)
SD (b)	6.74%	1.72%
Range (c)		
High	17/50	3/50
Low	4/49	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF UTERINE GLANDULAR TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Battelle Columbus Laboratories				
Chlorobenzene	50	0		
o-Dichlorobenzene	48	1	Endometrial gland	Adenoma, NOS
Overall Historical Incidence				
	1,125	1	Uterus, NOS	Adenoma, NOS
		2	Uterus, NOS	Papillary adenoma
		1	Uterus, NOS	Carcinoma, NOS
		7	Uterus, NOS	Adenocarcinoma
		2	Uterus/endometrium	Adenoma, NOS
		3	Uterus/endometrium	Adenocarcinoma, NOS
		1	Endometrial gland	Adenoma, NOS
Greatest Overall Historical Incidence		4/50		

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F9. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	4/50	2/50	6/50
o-Dichlorobenzene	4/50	4/50	8/50
TOTAL	8/100 (8.0%)	6/100 (6.0%)	14/100 (14.0%)
Overall Historical Incidence			
TOTAL	99/1,082 (9.1%)	(b) 58/1,082 (5.4%)	(b) 155/1,082 (14.3%)
SD (c)	4.77%	4.13%	6.31%
Range (d)			
High	10/50	7/50	13/50
Low	0/47	0/50	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes one adenocarcinoma, unclear primary or metastatic
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F10. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	1/50	0/50	1/50
o-Dichlorobenzene	3/47	0/47	3/47
TOTAL	4/97 (4.1%)	0/97 (0.0%)	4/97 (4.1%)
Overall Historical Incidence			
TOTAL	36/1,103 (3.3%)	16/1,103 (1.5%)	52/1,103 (4.7%)
SD (b)	2.81%	1.61%	3.46%
Range (c)			
High	5/50	2/49	6/50
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F11. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Leukemia	Lymphoma	Leukemia or Lymphoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	0/50	5/50	5/50
o-Dichlorobenzene	0/50	8/50	8/50
TOTAL	0/100 (0.0%)	13/100 (13.0%)	13/100 (13.0%)
Overall Historical Incidence			
TOTAL	6/1,090 (0.6%)	126/1,090 (11.6%)	132/1,090 (12.1%)
SD (b)	2.24%	5.63%	6.35%
Range (c)			
High	5/48	11/50	13/48
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F12. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Leukemia	Lymphoma	Leukemia or Lymphoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	1/50	11/50	12/50
o-Dichlorobenzene	2/49	11/49	13/49
TOTAL	3/99 (3.0%)	22/99 (22.2%)	25/99 (25.3%)
Overall Historical Incidence			
TOTAL	22/1,187 (1.9%)	237/1,187 (20.0%)	258/1,187 (21.7%)
SD (b)	3.13%	8.74%	9.11%
Range (c)			
High	5/48	17/50	20/49
Low	0/50	2/48	4/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F13. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	5/50	12/50	16/50
o-Dichlorobenzene	8/50	14/50	19/50
TOTAL	13/100 (13.0%)	26/100 (26.0%)	35/100 (35.0%)
Overall Historical Incidence			
TOTAL	133/1,084 (12.3%)	(b) 222/1,084 (20.5%)	340/1,084 (31.4%)
SD (c)	6.70%	7.90%	10.30%
Range (d)			
High	13/50	18/50	25/50
Low	0/50	4/50	5/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) One hepatoblastoma was also observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F14. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Battelle Columbus Laboratories (a)			
No tumors observed in 100 animals.			
Overall Historical Incidence			
	1,090	1	Adenoma, NOS

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F15. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus Laboratories			
Chlorobenzene	2/50	1/50	2/50
o-Dichlorobenzene	2/48	2/48	4/48
TOTAL	4/98 (4.1%)	3/98 (3.1%)	6/98 (6.1%)
Overall Historical Incidence			
TOTAL	47/1,176 (4.0%)	34/1,176 (2.9%)	80/1,176 (6.8%)
SD (b)	2.55%	2.18%	3.37%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F16. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Carcinoma or Adenocarcinoma in Vehicle Controls
Historical Incidence at Battelle Columbus Laboratories	
Chlorobenzene	1/50
o-Dichlorobenzene	0/49
TOTAL	1/99 (1.0%)
Overall Historical Incidence	
TOTAL	(b) 15/1,187 (1.3%)
SD (c)	1.55%
Range (c)	
High	2/50
Low	0/97

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes one carcinoma, NOS and one adenosquamous carcinoma. All other tumors are adenocarcinoma, NOS.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F17. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Battelle Columbus Laboratories		
No ovarian tumors observed in 100 animals		
Overall Historical Incidence		
1,028	1	Adenoma, NOS
	1	Papillary adenoma
	1	Cystadenoma, NOS
	1	Luteoma
	1	Sertoli cell tumor
	1	Teratoma, benign
	2	Granulosa cell tumor
	1	Granulosa cell carcinoma
	1	Teratoma, NOS
	1	Adenocarcinoma, NOS
	1	Teratoma, malignant

(a) Data as of March 16, 1983, for studies of at least 104 weeks. No more than two ovarian tumors were present in any single control group.

TABLE F18. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Male Adenoma	Female Adenoma
Historical Incidence at Battelle Columbus Laboratories		
Chlorobenzene	1/50	0/50
o-Dichlorobenzene	0/50	0/49
TOTAL	1/100 (1.0%)	0/99 (0.0%)
Overall Historical Incidence		
TOTAL	(b) 32/1,090 (2.9%)	(c) 11/1,187 (0.9%)
SD (d)	2.88%	1.33%
Range (e)		
High	(b) 4/50	(c) 2/50
Low	0/50	0/97

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) One cystadenoma and two carcinomas were also observed. Greatest combined incidence observed is 5/50.
(c) One cystadenoma and one carcinoma were also observed. Greatest combined incidence observed is 3/50.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F19. HISTORICAL INCIDENCE OF ADRENAL GLAND PHEOCHROMOCYTOMAS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Male	Female
Historical Incidence at Battelle Columbus Laboratories		
Chlorobenzene	2/50	0/49
o-Dichlorobenzene	4/50	1/48
TOTAL	6/100 (6.0%)	1/97 (1.0%)
Overall Historical Incidence		
TOTAL	(b) 24/1,037 (2.3%)	11/1,056 (1.0%)
SD (c)	2.57%	1.74%
Range (d)		
High	(b) 4/49	2/36
Low	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) One pheochromocytoma, malignant was also observed. The greatest observed combined incidence is 5/49.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F20. HISTORICAL INCIDENCE OF STOMACH TUMORS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Site/Diagnosis
Historical Incidence at Battelle Columbus Laboratories			
No tumors observed in 100 males or 99 females			
Overall Historical Incidence			
MALE	1,055		
			Forestomach
		4	Squamous cell papilloma
		3	Squamous cell carcinoma
FEMALE	1,077		
			Forestomach
		4	Squamous cell papilloma
			Glandular Stomach
		1	Adenomatous polyp
		1	Adenoma
		1	Adenocarcinoma

(a) Data as of March 16, 1983, for studies of at least 104 weeks

TABLE F21. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Battelle Columbus Laboratories			
MALE RATS			
No tumors were observed in 100 animals.			
FEMALE RATS			
Chlorobenzene	50	0	
o-Dichlorobenzene	50	1	Adenocarcinoma, NOS
MALE MICE			
No tumors were observed in 100 animals.			
FEMALE MICE			
No tumors were observed in 99 animals.			
Overall Historical Incidence			
MALE RATS			
	1,146	1	Carcinoma, NOS
		3	Squamous cell carcinoma
FEMALE RATS			
	1,147	1	Carcinoma, NOS
		2	Squamous cell carcinoma
		1	Basal cell carcinoma
		1	Adenocarcinoma, NOS
MALE MICE			
	1,090	0	
FEMALE MICE			
	1,187	1	Adenoma, NOS

(a) Data as of March 16, 1983, for studies of at least 104 weeks

APPENDIX G

GENETIC TOXICOLOGY OF BENZENE, CATECHOL, AND HYDROQUINONE

TABLE G1. INDUCTION OF MICRONUCLEI IN PERIPHERAL NORMOCHROMATIC ERYTHROCYTES (NCE's) OF B6C3F$_1$ MICE BY BENZENE

Dose (mg/kg)	Scorer	Micronucleated NCE/1,000 NCE (a) 120 Days Male	120 Days Female	54 Weeks Male	54 Weeks Female	103 Weeks Male	103 Weeks Female
0	1	1.60 ± 0.73	1.00 ± 0.28	1.40 ± 0.25	1.30 ± 0.35	1.50 ± 0.43	1.40 ± 0.35
	2	0.80 ± 0.52	1.20 ± 0.44	0.70 ± 0.25	1.10 ± 0.41	1.40 ± 0.43	0.30 ± 0.15
	Pooled	1.20 ± 0.46	1.10 ± 0.26	1.05 ± 0.19	1.20 ± 0.27	1.45 ± 0.30	0.85 ± 0.23
25	1	2.60 ± 0.87	(b) 0.60 ± 0.22	1.40 ± 0.38	1.10 ± 0.26	1.60 ± 0.32	0.80 ± 0.30
	2	(b) 2.40 ± 0.60	1.80 ± 0.33	1.00 ± 0.25	1.30 ± 0.40	1.80 ± 0.40	(c) 1.40 ± 0.45
	Pooled	(b) 2.50 ± 0.54	1.20 ± 0.28	1.20 ± 0.23	1.20 ± 0.24	1.70 ± 0.25	1.10 ± 0.28
50	1	(c) 5.00 ± 1.10	2.00 ± 0.40	2.20 ± 0.46	1.20 ± 0.34	(b,d) 2.80 ± 0.77	1.40 ± 0.05
	2	(b) 3.20 ± 0.66	1.60 ± 0.67	1.50 ± 0.29	0.90 ± 0.39	(b,d) 2.70 ± 0.49	(c) 1.70 ± 0.07
	Pooled	(c) 4.10 ± 0.70	1.80 ± 0.40	(b) 1.85 ± 0.29	1.05 ± 0.26	(b,d) 2.75 ± 0.46	(b) 1.55 ± 0.45
100	1	(c) 4.60 ± 1.15	1.00 ± 0.28	(c) 4.80 ± 0.78	2.00 ± 0.53	2.30 ± 0.44	2.00 ± 0.37
	2	(c) 7.00 ± 0.40	1.00 ± 0.28	(c) 4.70 ± 0.58	1.80 ± 0.51	(c) 3.10 ± 0.78	(c) 1.80 ± 0.34
	Pooled	(c) 5.80 ± 0.72	1.00 ± 0.20	(c) 4.75 ± 0.48	(b) 1.90 ± 0.37	(b) 2.70 ± 0.46	(b) 1.90 ± 0.25
200	1	(c) 5.80 ± 0.82	2.00 ± 0.63				
	2	(c) 7.20 ± 1.58	3.00 ± 0.49				
	Pooled	(c) 6.50 ± 0.92	2.00 ± 0.40				
400	1	(c) 8.00 ± 1.41	(b) 2.60 ± 0.22				
	2	(c) 9.00 ± 1.20	(b) 3.60 ± 1.04				
	Pooled	(c) 8.50 ± 1.10	(c) 3.10 ± 0.56				
600	1	(c) 10.60 ± 1.56	(c) 3.80 ± 0.66				
	2	(c) 8.00 ± 2.04	(b) 3.60 ± 0.36				
	Pooled	(c) 9.30 ± 1.35	(c) 3.70 ± 0.72				

(a) Values are mean ± standard error of the mean. One thousand normochromatic cells were scored per animal by each scorer according to MacGregor et al. (1983). Five animals per sex/dosed group were scored by each scorer from the 120-day exposures and 10 by each scorer from the 54- and 103-week exposures. Dosed groups were compared with the concurrent undosed sex/dose/time group by the binomial comparison of Kastenbaum and Bowman (1970).
(b) $P \leq 0.05$
(c) $P \leq 0.01$
(d) One outlier was excluded from this group. The values excluded were 12 and 14 per 1,000 NCE by scorers 1 and 2, respectively.

TABLE G2. MUTAGENICITY OF CATECHOL IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a)		
		−S9	+S9 (rat)	+S9 (hamster)
TA 100	0	124 ± 9.9	138 ± 7.0	131 ± 7.3
	33	126 ± 1.5	132 ± 12.8	125 ± 8.7
	100	142 ± 12.2	129 ± 2.8	141 ± 6.9
	333	124 ± 6.6	140 ± 10.9	148 ± 9.0
	1,000	83 ± 8.0	154 ± 19.4	161 ± 15.3
	3,333	Toxic	155 ± 15.7	167 ± 8.1
TA1535	0	25 ± 6.0	12 ± 2.9	14 ± 0.9
	33	22 ± 1.3	15 ± 0.9	13 ± 2.9
	100	20 ± 3.5	10 ± 1.7	14 ± 2.5
	333	18 ± 0.3	16 ± 0.3	13 ± 2.1
	1,000	5 ± 1.3	23 ± 4.0	16 ± 1.9
	3,333	Toxic	20 ± 2.0	20 ± 3.2
TA1537	0	11 ± 2.7	20 ± 0.3	26 ± 3.5
	33	12 ± 1.0	20 ± 3.2	21 ± 2.8
	100	12 ± 1.8	27 ± 1.9	24 ± 1.3
	333	12 ± 1.5	23 ± 3.5	22 ± 3.5
	1,000	12 ± 1.8	23 ± 1.9	23 ± 4.0
	3,333	Toxic	16 ± 3.7	20 ± 4.3
TA98	0	25 ± 2.4	22 ± 5.0	35 ± 3.4
	33	18 ± 4.1	35 ± 4.7	37 ± 4.1
	100	18 ± 1.5	31 ± 6.5	30 ± 2.8
	333	17 ± 0.7	28 ± 1.8	28 ± 2.3
	1,000	25 ± 2.3	24 ± 1.9	34 ± 2.5
	3,333	Toxic	36 ± 1.9	36 ± 2.4

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (water) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). 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 h (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE G3. MUTAGENICITY OF HYDROQUINONE IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a)		
		−S9	+S9 (rat)	+S9 (hamster)
TA100	0	100 ± 3.0	121 ± 9.7	90 ± 0.0
	10	97 ± 1.5	122 ± 4.0	122 ± 16.7
	33	107 ± 6.7	127 ± 7.8	108 ± 15.7
	100	108 ± 3.9	92 ± 2.6	107 ± 10.1
	333	Toxic	80 ± 5.5	112 ± 13.7
	666	--	115 ± 13.3	123 ± 16.0
TA1535	0	15 ± 1.2	7 ± 2.0	7 ± 0.3
	10	15 ± 2.7	11 ± 2.5	9 ± 1.8
	33	9 ± 1.2	11 ± 1.3	8 ± 0.9
	100	8 ± 1.2	7 ± 0.6	11 ± 2.3
	333	Toxic	8 ± 1.3	11 ± 0.3
	666	--	9 ± 1.2	8 ± 2.1
TA1537	0	8 ± 0.3	7 ± 1.5	8 ± 2.2
	10	7 ± 0.7	6 ± 2.0	7 ± 2.0
	33	6 ± 0.9	7 ± 1.2	8 ± 0.7
	100	5 ± 1.8	7 ± 1.2	10 ± 2.7
	333	Toxic	6 ± 1.2	6 ± 1.5
	666	--	8 ± 0.7	8 ± 0.9
TA98	0	20 ± 1.5	23 ± 1.7	30 ± 0.9
	10	19 ± 1.7	25 ± 5.5	30 ± 1.0
	33	22 ± 3.7	26 ± 3.0	29 ± 0.6
	100	18 ± 0.5	21 ± 5.9	25 ± 0.9
	333	Toxic	25 ± 2.2	26 ± 4.1
	666	--	17 ± 2.6	29 ± 1.2

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (water) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). 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 h (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE G4. CYTOGENETIC EFFECTS OF HYDROQUINONE IN CHINESE HAMSTER OVARY (CHO) CELLS

Sister-Chromatid Exahanges (a)

−S9		+S9 (b)	
Dose (µg/ml)	SCE/Cell	Dose (µg/ml)	SCE/Cell
DMSO (10 µl)	7.7	DMSO (10 µl)	9.3
0.50	11.2	600	15.4
1.67	17.7	700	18.5
5.00	20.8	800	17.6
Mitomycin C (0.005)	33.3	Cyclophosphamide (1.5)	25.1

Chromosomal Aberrations (c)

−S9		+S9 (b)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO (10 µl)	3 (3)	DMSO (10 µl)	1 (1)
5.0	2 (2)	150	5 (4)
7.5	2 (2)	450	22 (17)
10.0	>4 (4)	600	>29 (19)
20.0	5 (8)		
Mitomycin C (1)	20 (20)	Cyclophosphamide (25)	20 (18)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hours at 37° C. BrdU then was added, and incubation continued for 2 hours. Cells were washed, fresh medium containing BrdU (0.10 µM) and colcemid (0.1 µg/ml) was added, and incubation was continued for 2-3 hours. Cells then were collected by mitotic shake-off, treated for 3 minutes with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978). In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 mM BrdU was added. Cells were incubated for another 26 hours, with colcemid (0.1 µg/ml) present for the final 2-3 hours.
(b) S9 from the livers of Aroclor 1254-induced male Sprague-Dawley rats
(c) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After another 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Cells then were washed, medium was added, and incubation continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above.

APPENDIX H

CHEMICAL CHARACTERIZATION OF BENZENE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. AB223 Performed by the Analytical Chemistry Laboratory

A. Physical Properties

1. Boiling Point:

Determined	Literature Values
80.0°-80.5° C (visual micro-boiling point)	80.1° C (Merck Index, 1976)

2. Density:

Determined	Literature Values
d_{22}^{24}: 0.8719 ± 0.0018	d_{4}^{15}: 0.8787 (Merck Index, 1976)

3. Appearance: Clear, colorless liquid

B. Spectral Data

1. Infrared

	Determined	Literature Values
a. Instrument:	Beckman IR-12	
b. Cell:	Thin film between silver chloride plates	
c. Results:	See Figure 9	Consistent with spectrum (Sadtler Standard Spectra)

2. Ultraviolet/Visible

	Determined	Literature Values
a. Instrument:	Cary 118 There were no absorbances from 800-350 nm (visible region)	
b. Solvent:	Cyclohexane	Cyclohexane

c. Results:

Determined		Literature Values	
λ_{max} (nm)	ε_{max}	λ_{max} (nm)	ε_{max}
268	8.6 ± 0.6	268	13.54
261	116.1 ± 9.6	260	149.00
254	167.0 ± 18.8	254	212.21
248	139.0 ± 11.8	250	168.56
243	87.6 ± 7.9	243	99.33
		239	52.68*
		234	31.60*

* Broad and poorly resolved
(Calculated from literature spectrum: Sadtler Standard Spectra)

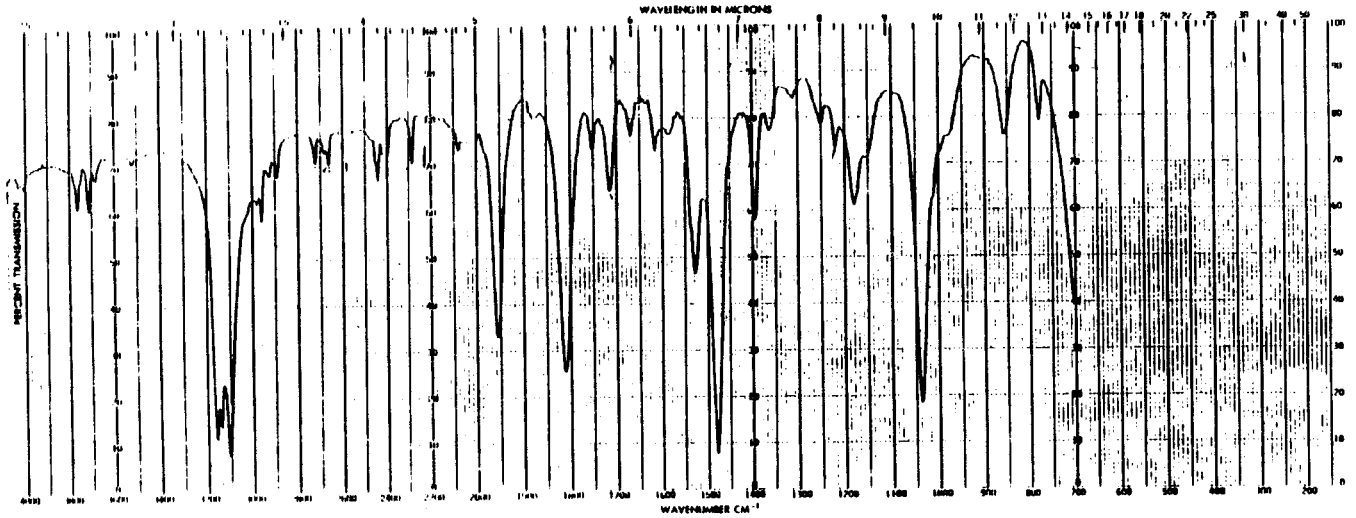


FIGURE 9. INFRARED ABSORPTION SPECTRUM OF BENZENE (LOT NO. AB223)

3. **Nuclear Magnetic Resonance**

	Determined	Literature Values
a. Instrument:	Varian EM-360-A	
b. Solvent:	Neat, with tetramethylsilane internal standard	
c. Assignments:	See Figure 10	Consistent with spectrum (Sadtler Standard Spectra)
d. Chemical Shift (δ):	s, 7.17 ppm	
e. Integration Ratios:	6.00	

C. Elemental Analysis

Element	C	H
Theory	92.26	7.74
Determined	92.44 92.48	7.72 7.65

D. Chromatographic Analyses

1. Gas Chromatography

a. System 1

Instrument: Varian 3700
Detector: Flame ionization
Column: 10% Carbowax 20M-TPA on 80/100 Chromasorb W(AW), 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 250° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 5 min at 50° C, 50°-200° C at 10°/min
Sample injected: Neat liquid (6 µl) and 1.0% and 0.4% in hexanes to quantitate the major peak and check for detector overload.

Results: Major peak and four impurities. The combined area of all four impurities was 0.2% of the major peak area. All impurities eluted before the major peak.

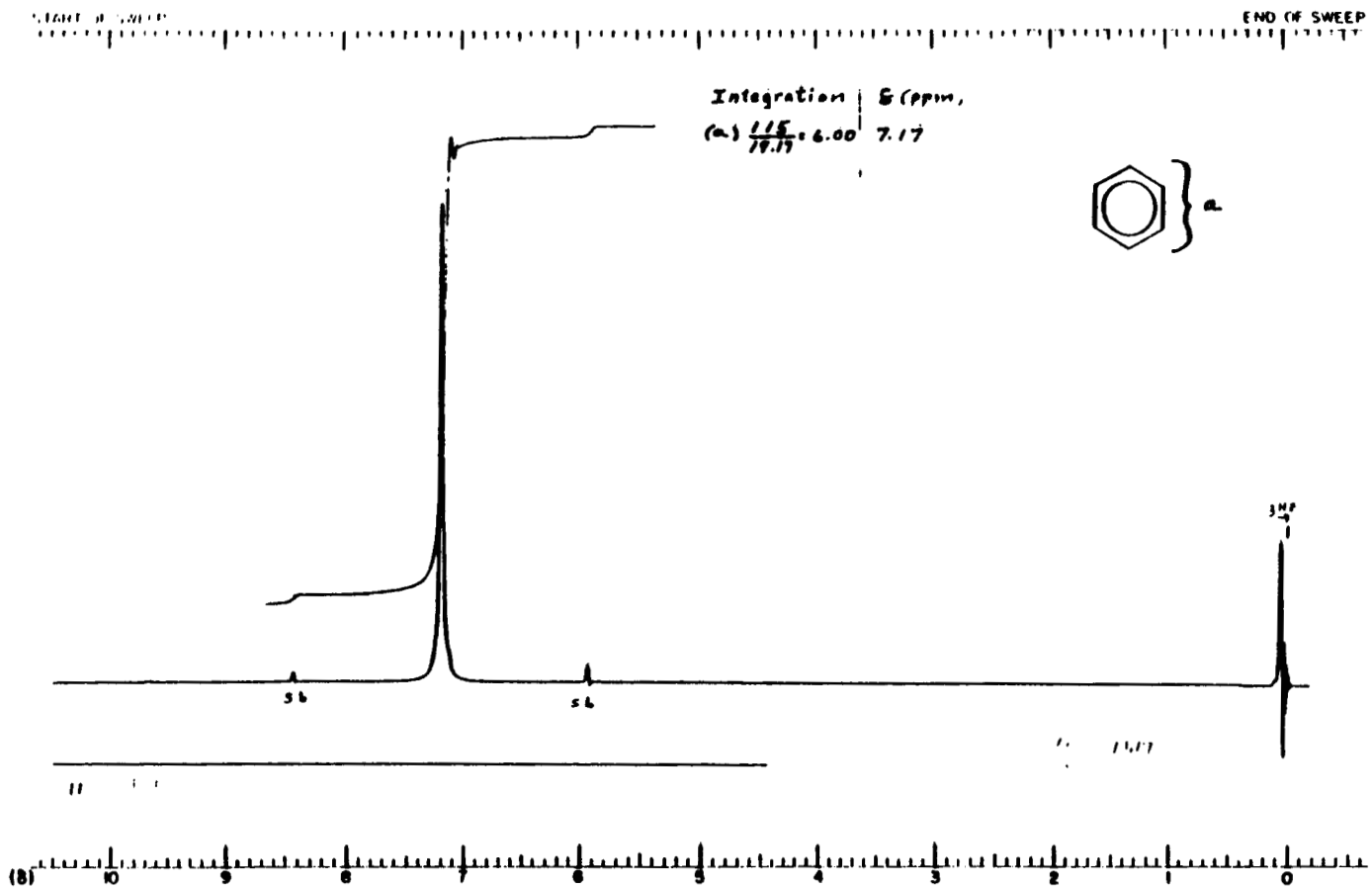


FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BENZENE (LOT NO. AB223)

Lot No. AB223

Peak No.	Retention Time (min)	Retention Time Relative to Benzene	Area (percent of benzene)
1	0.55	0.18	0.03
2	0.74	0.23	0.05
3	0.94	0.30	0.08
4	1.17	0.37	0.04
5	3.16	1.00	100.00

Lot No. AB490

Peak No.	Retention Time (min)	Retention Time Relative to Benzene	Area (percent of benzene)
1	0.63	0.20	0.02
2	0.79	0.25	0.09
3	1.00	0.32	0.14
4	1.26	0.40	0.04
5	3.16	1.00	100.00

b. System 2

Instrument: Varian 3700
Detector: Flame ionization
Column: GP 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 250° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 5 min at 50° C, 50°-170° C at 10°/min
Sample injected: Neat liquid (7 µl) and 1.0% and 0.5% in methanol to quantitate the major peak and check for detector overload.

Results: Major peak and five impurities. The combined area of all five impurities was <0.09% of the major peak area. One impurity eluted before the major peak. The other four impurities eluted after the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Benzene	Area (percent of benzene)
1	5.0	0.77	0.01
2	6.5	1.00	100.00
3	8.2	1.26	0.01
4	9.1	1.40	0.02
5	10.8	1.65	0.04
6	12.8	1.97	0.01

F. Conclusions: The elemental analyses for carbon and hydrogen were in agreement with the theoretical values. Gas chromatography by one system indicated four impurities with total combined areas of 0.2% of the major peak area. A second gas chromatographic system indicated five impurities that totaled <0.09% of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure.

II. Test Chemical Stability Study of Lot No. AB223 Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Samples of benzene were stored for 2 weeks at – 20°, 5°, 25°, or 60° C in glass tubes with Teflon®-lined lids.

B. Analytical Method: Samples stored at each of the above temperatures were analyzed by making 1.0% solutions of the samples in hexane containing 1.0% *n*-decane internal standard and comparing by the following gas chromatographic system.

1. **Instrument:** Varian 3700
2. **Detector:** Flame ionization
3. **Column:** 10% Carbowax 20M-TPA on 80/100 Chromasorb W(AW), 1.8 m × 4 mm ID, glass
4. **Inlet temperature:** 200° C
5. **Detector temperature:** 250° C
6. **Carrier gas:** Nitrogen
7. **Carrier flow rate:** 70 ml/min
8. **Oven temperature program:** 50° C, isothermal

C. Results: Retention times were 3.2 minutes for benzene and 5.3 minutes for *n*-decane. The areas of benzene peaks were compared with the area of the *n*-decane peak in the same injection. These areas, adjusted for the weight of the sample, were then compared with the area of the benzene peak of the sample stored at – 20° C.

Storage Temperature	Percent Benzene
– 20° C	100.0 ± 1.3
+ 5° C	100.4 ± 1.3
+25° C	100.0 ± 1.3
+60° C	100.0 ± 1.3

D. Conclusion: Benzene is stable as the bulk chemical for 2 weeks at temperatures of up to 60° C.

III. Test Chemical Stability Study of Lot No. AB223 Performed by the Testing Laboratory

A. Storage Conditions: Reference samples of benzene were stored in screwcap glass vials at room temperature. The bulk chemical was also stored at room temperature.

B. Analytical Methods

1. Gas Chromatography

a. Instrument: Varian 2100 Gas Chromatograph with CDS 111L Data System
b. Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport
c. Detector temperature: 230° C
d. Injector temperature: 150° C
e. Temperature program: 50° C for 3 min, then 50°-170° C at 6°/min
f. Carrier gas: Nitrogen
g. Carrier flow rate: 20 ml/min
h. Sample size: 1 µl
i. Concentrations: Neat liquid and 1.0% benzene in methanol

2. **Infrared:** Digilab FTS-10 (Fourier Transform IR System); samples run as a liquid between plates.

C. Results

1. Gas Chromatography

Date	Percent Impurities	Percent Purity (a)
11/07/79	<0.09	99.94
12/10/79	<0.09	99.94
5/09/80	<0.09	99.94
7/24/80	<0.07	99.94
12/29/80	<0.07	99.93
5/01/81	<0.08	99.92
8/10/81	<0.07	99.94
8/08/82	<0.08	99.93

(a) Relative to total peak area

2. **Infrared:** All spectra were similar to those prepared by the analytical chemistry laboratory and were identical to those of the reference sample.

D. Conclusion: No measurable degradation of the bulk chemical was observed over the course of the 2-year studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Sample and Storage: A stock solution was prepared by pipetting 2 ml (1.75 ± 0.01 g) of benzene into a 60-ml septum vial and adding 43.9407 ± 0.0001 g of corn oil. The vial was sealed, shaken on a vortex mixer for 1 minute, and placed in an ultrasonic vibratory bath for 1 minute. The final benzene concentration was 3.83% ± 0.02% (w/w). As soon as the solution had been prepared, 10 accurately weighed 2.0-g aliquots were removed and sealed in separate 60-ml septum vials (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Bio-medical Products, Inc.). Duplicate aliquots were used as initial, or zero-time, samples and for storage at room temperature (25° C) for 1, 4, 5, and 7 days, respectively.

B. Sample Extraction and Analysis: Extracting solvent containing an internal reference standard was prepared by pipetting 3 ml (2.60 ± 0.01 g) of toluene into a 1-liter volumetric flask and filling to the mark with absolute methanol. Concentration of reference standard: 2.60 ± 0.01 mg/ml.

To extract each sample aliquot, the septum vial was opened, 40 ml of the extracting solvent was added by volumetric pipette, and the vial was immediately resealed. The corn oil/methanol mixture was manually shaken for 1 minute, agitated on a vortex mixer for 1 minute, and placed in an ultrasonic bath for 2 minutes. After the bulk of the two phases had separated, the methanol layer was centrifuged for 5 minutes to clarify it, and a 5-ml aliquot was transferred to an 8.5-ml septum vial. This aliquot of the methanol solution was analyzed by the gas chromatographic system outlined below:

1. **Instrument:** Bendix 2500 with Hewlett-Packard® 3380A Automatic Integrator
2. **Column:** 20 SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 4 mm ID, glass.
3. **Detection:** Flame ionization
4. **Temperatures:**
   a. Inlet, 150° C
   b. Oven, 70° C, isothermal
   c. Detector, 225° C
5. **Carrier gas:** Nitrogen
6. **Flow rate:** 40 ml/min
7. **Retention times:**
   a. Test chemical, 2.6 min
   b. Reference standard, 5.6 min

C. Quality Control Protocols: Analyses were performed in duplicate with toluene as an internal reference standard. Recovery studies (zero-time samples) were performed in duplicate at the same concentration as the test samples, both at the start and at the end of the 7-day period. Gas chromatographic linearity was determined with standard solutions in methanol at 1.97, 2.81, and 3.51 mg/ml concentrations from the benzene and 1.94, 2.77, and 3.46 mg/ml for the toluene internal reference. The least-squares plot correlation coefficients were 0.998 for the test chemical and 0.996 for the internal reference (effectively 1.0, linear).

D. Results:

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture(a) (b)
1	(c) 3.78 ± 0.04
4	3.80 ± 0.04
5	3.83 ± 0.04
7	3.82 ± 0.04

(a) Zero-time recovery yield, 100.0% ± 0.9%.
(b) Target concentration of chemical in corn oil, 3.83% ± 0.02%.
(c) Mean ± standard deviation

E. Conclusion: Benzene mixed with corn oil at a concentration of 4% is stable when stored at room temperature (25° C) for 7 days.

II. Studies Conducted at the Testing Laboratory

Preparation Procedure: A weighed quantity of benzene was added to the appropriate volume of corn oil and mixed in a graduated mixing cylinder by stoppering the cylinder and inverting 21 times. The total quantity of solution mixed weekly for each concentration varied according to the growth stage of the animals. As an example, the highest dose concentration for the mice was prepared first by weighing out and mixing 5.0 g of the chemical with sufficient corn oil to make a volume of 250 ml (20 mg/ml). When mixed, 125 ml was withdrawn, added to 125 ml of corn oil, and mixed to give a second dose concentration of 10 mg/ml. One hundred twenty-five milliliters was removed from this solution and combined with 125 ml corn oil to yield a third dose with a concentration of 5 mg/ml.

Each week, separate batches were mixed for each concentration. After they were mixed, five daily aliquots were dispensed to glass containers (one for each sex and each concentration) and stored at room temperature until the day of first use. Dose mixtures were routinely prepared no more than 7 days before the first day of use and were routinely used within 2 weeks of preparation.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Testing Laboratory

Procedure: Standards were prepared by serial dilution of 40.0, 20.0, 10.0, and 5.0 mg benzene per 1.0 ml corn oil. One-ml aliquots of standards and samples were extracted with 9.0 ml of extracting solvent (a). The mixtures were vortexed and centrifuged, and a 5.0-ml portion of the clear extracted solvent was removed and analyzed by gas chromatography. Concentrations were determined by the internal standard calculation method, and analyses were done in duplicate.

Instrument: Varian Aerograph 2100-Gas Chromatograph with CDS 111L Data System
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport
Detector temperature: 230° C
Injector temperature: 150° C
Temperature program: 70° C isothermal
Carrier gas: Nitrogen
Flow rate: 40 ml/min
Sample size: 2 µl

(a) Methanol containing toluene as an internal standard at a concentration of 2.6 mg/ml

II. Analytical Chemistry Laboratory

Procedure

A. **Preparation of Standard Spiked Corn Oil:** Two standard solutions of benzene were prepared independently. These solutions were further diluted with methanol to span the range of the sample. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. The spiked corn oil and the corn oil blank were extracted immediately and were analyzed according to the procedure below.

B. **Preparation of the Referee Sample:** Triplicate weights of the dosed referee corn oil sample (approximately 2 g each) were transferred to individual 35-ml septum vials and were weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial; then the samples were extracted immediately and were analyzed according to the procedure below.

C. **Analysis:** The vials were sealed, vigorously agitated for 10 seconds on a vortex mixer, and then shaken for 15 minutes on a Burrell Model 75 Wrist-Action® shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of the upper methanol layer from each vial was combined with 5 ml of internal standard solution (as above) in individual 35-ml septum vials. The vials were sealed, and the solutions were thoroughly mixed; then the benzene content of each solution was determined by gas chromatography.

1. **Instrument:** Varian 3700 Gas Chromatograph with CDS 111-C integrator
2. **Column:** 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
3. **Detection:** Flame ionization
4. **Detector temperature:** 220° C
5. **Inlet temperature:** 150° C
6. **Temperature program:** 70° C, isothermal
7. **Carrier gas:** Nitrogen
8. **Flow rate:** 30 ml/min
9. **Volume of solution injected:** 3 µl
10. **Retention times:** Benzene--2.4 min; toluene internal standard--4.8 min

D. **Quality Assurance Measures:** The dosed referee corn oil sample was analyzed in triplicate, and the corn oil blank sample was analyzed once. Individually spiked portions of undosed corn oil (six concentrations) prepared from two independently weighed standards were used for obtaining standard curve data. The dosed referee corn oil sample, spiked corn oil standards, and corn oil blank samples were all extracted and analyzed according to the same procedure. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

Results were computed from the linear regression equation obtained by plotting the ratio of the peak area of each spiked corn oil sample to the peak area of the internal standard versus the milligrams of chemical in the respective spiked corn oil sample. The linearity of the standard curve data was evaluated by the regression equation.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE SEVENTEEN-WEEK GAVAGE STUDIES OF BENZENE

Date Mixed	Concentration (a) of Benzene in Corn Oil for Target Concentration (120 mg/ml)
1/24/79	128 mg/ml

(a) Results of duplicate analysis

TABLE K2. ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

Date Mixed	Concentration (a) of Benzene in Corn Oil for Target Concentration (mg/ml)			
	5	10	20	40
12/4/79	5.4	9.5	19.1	38.2
1/24/80	4.8	10.9	21.6	39.3
3/19/80	5.1	10.1	20.2	38.0
6/5/80	5.0	10.9	20.6	40.5
7/14/80	5.4	11.0	21.4	41.7
9/11/80	4.7	9.8	20.4	40.9
11/6/80	5.1	10.6	20.1	37.1
1/8/81	5.2	10.3	20.7	41.3
2/26/81	5.5	10.3	21.4	37.5
4/23/81	5.4	10.7	21.1	37.2
6/4/81	5.4	10.9	19.8	38.9
8/13/81	5.2	10.7	21.2	41.5
10/15/81	5.2	10.0	20.2	41.0
12/17/81	4.6	9.4	20.4	--
Mean (mg/ml)	5.1	10.4	20.6	39.5
Standard deviation	0.28	0.54	0.70	1.75
Coefficient of variation (percent)	5.5	5.2	3.4	4.4
Range (mg/ml)	4.6-5.5	9.4-11.0	19.1-21.6	37.1-41.7

(a) Results of duplicate analysis

TABLE K3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Testing Laboratory	Referee Laboratory (a)
3/19/80	10.0	10.1	10.1
7/14/80	40.0	41.7	37.1
2/26/81	20.0	21.4	(b) 16.0
8/13/81	5.0	5.2	5.4

(a) Results of triplicate analysis
(b) Analyzed 19 days after mixing; low value may be due to evaporation.

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. Methods

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

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

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

II. Results

See Table L1.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	9/10	KRV
12	7/10	KRV
18	7/10	KRV
24	7/10	KRV
MICE		
6	0/10	None positive
12	0/8	None positive
18	1/10	PVM
	1/10	REO3
24	1/10	MVM

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

APPENDIX M

RESULTS OF HEMATOLOGIC DETERMINATIONS IN RATS AND MICE IN THE SEVENTEEN-WEEK GAVAGE STUDIES OF BENZENE

TABLE M1. HEMATOLOGIC DETERMINATIONS IN RATS IN THE SEVENTEEN-WEEK GAVAGE STUDIES OF BENZENE (a)

	Doses (mg/kg)						
	0	25	50	100	200	400	600
MALE							
Day 60							
WBC mean	6.4				(b) 2.5		(b) 1.7
SEM	1.2				0.1		0.2
LYM mean	5.8				(b) 2.0		(b) 1.3
SEM	1.1				0.1		0.2
Day 120							
WBC mean	5.0 (4)	(b) 7.0	5.7	6.0	5.2	3.5 (4)	3.1 (1)
SEM	0.5	0.3	0.3	0.8	0.5	0.5	
LYM mean	4.1 (4)	5.1	3.9	3.9	3.4	(b) 2.3 (4)	2.4 (1)
SEM	0.5	0.3	0.2	0.5	0.4	0.3	
FEMALE							
Day 60							
WBC mean	4.3				(b) 2.3		(b) 1.7
SEM	0.9				0.4		0.1
LYM mean	3.8				(b) 1.9		(b) 1.5
SEM	0.8				0.3		0.1
Day 120							
WBC mean	8.1 (4)	(b) 6.2	(b) 4.9	(b) 5.0	(b) 4.8	(b) 3.4	(b) 3.8
SEM	0.6	0.6	0.3	0.3	0.3	0.2	0.3
LYM mean	6.6 (4)	(b) 4.7	(b) 3.9	(b) 3.6	(b) 3.7	(b) 2.7	(b) 2.8
SEM	0.5	0.4	0.3	0.3	0.2	0.2	0.3

(a) Means are /mm^3 $\times$ 10^3 for white blood cells (WBC) and lymphocytes (LYM) $\pm$ standard error of the mean (SEM). N = 5 for all determinations except as noted in parentheses.
(b) $P<0.05$ for dosed vs vehicle control by Dunnett's test (Miller, 1981)

TABLE M2. HEMATOLOGIC DETERMINATIONS IN MICE IN THE SEVENTEEN-WEEK GAVAGE STUDIES OF BENZENE (a)

	Doses (mg/kg)						
	0	25	50	100	200	400	600
MALE							
Day 60							
WBC mean	14.4				11.8		13.6
SEM	2.1				2.5		2.8
LYM mean	11.4				8.8		10.7
SEM	1.7				1.7		2.0
Day 120							
WBC mean	6.7	5.4	(b) 4.4 (4)	(b) 3.3	(b) 3.8	(b) 2.9	(b) 3.0
SEM	0.1	0.6	0.3	0.1	0.2	0.3	0.4
LYM mean	5.2	4.2	(b) 3.1 (4)	(b) 2.2	(b) 2.3	(b) 1.6	(b) 1.6
SEM	0.1	0.6	0.4	0.2	0.2	0.04	0.3
FEMALE							
Day 60							
WBC mean	8.2 (4)				8.1		11.5
SEM	2.5				2.0		2.9
LYM mean	6.5 (4)				6.7		9.6
SEM	1.8				1.6		2.6
Day 120							
WBC mean	6.0	4.2	4.6	3.7	4.6	3.8	(b) 2.7
SEM	1.6	0.2	0.2	0.4	0.4	0.4	0.3
LYM mean	4.7	3.0	3.6	2.8	3.2	(b) 2.6	(b) 1.8
SEM	1.2	0.2	0.3	0.3	0.3	0.2	0.2

(a) Means are /mm^3 $\times$ 10^3 for white blood cells (WBC) and lymphocytes (LYM) $\pm$ standard error of the mean (SEM). N = 5 for all determinations except as noted in parentheses.
(b) $P<0.05$ for dosed vs vehicle control by Dunnett's test (Miller, 1981)

APPENDIX N

RESULTS OF HEMATOLOGIC DETERMINATIONS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZENE

APPENDIX N. HEMATOLOGIC DETERMINATIONS

I. SUMMARY OF RESULTS

A. White Blood Cells--Rats

For males, significant dose and interaction terms ($P<0.02$) in the analyses of variance (Table N1) suggest a strong but temporally variable dose effect. The plot of the dose group means (Figure 11) over time gives evidence of a compound-induced depression of white blood cell (WBC) counts over the first 18 months of study (Table N2). Although there is a difference in vehicle control group means for groups B and C at 12 months, there is reasonable consistency in the relationship of vehicle control and dosed group means at this time. Dosed females also exhibited lowered WBC counts relative to those of vehicle controls for the first year of study, but this result is questionable because of evidence of a dose-related predosing (time 0) depression in WBC count. An inconsistent pattern of response in the last half of the study gives little suppport for systematic dose-related differences in WBC's for females during this period. Analysis specific to lymphocytes is presented in Tables N3 and N4.

TABLE N1. WHITE BLOOD CELLS IN RATS: ANALYSES OF VARIANCE

	MALE				FEMALE			
SOURCE	DF (a)	MS (b)	F	PROB>F	DF (a)	MS (b)	F	PROB>F
0-3 MONTHS (GROUP C)								
DOSE	3	13.31	10.12	<0.001	3	14.22	9.50	<0.001
ANIMAL (DOSE)	36	1.32			36	1.50		
TIME	1	7.75	3.79	0.060	1	65.50	57.89	<0.001
DOSETIME	3	15.45	7.56	<0.001	3	5.39	4.76	0.007
ERROR	35	2.04			35	1.13		
6-9 MONTHS (GROUP C)								
DOSE	3	24.63	31.64	<0.001	3	3.56	5.50	0.003
ANIMAL (DOSE)	32	0.78			35	0.65		
TIME	1	12.30	25.27	<0.001	1	23.38	54.44	<0.001
DOSETIME	3	2.05	4.20	0.019	3	0.20	0.46	0.715
ERROR	19	0.49			27	0.43		
12 MONTHS (GROUP C)								
DOSE	3	10.93	9.74	<0.001	3	1.74	8.33	<0.001
ERROR	21	1.12			27	0.21		
12-21 MONTHS (GROUP B)								
DOSE	3	33.70	17.45	<0.001	3	3.03	1.19	0.329
ANIMAL (DOSE)	30	1.93			35	2.56		
TIME	3	9.38	15.74	<0.001	3	0.93	1.09	0.357
DOSETIME	9	3.29	5.52	<0.001	9	1.29	1.51	0.155
ERROR	57	0.60			94	0.85		
24 MONTHS (GROUP B)								
DOSE	3	0.52	0.39	0.762	3	2.37	0.86	0.477
ERROR	10	1.32			23	2.76		
24 MONTHS (GROUP A)								
DOSE	3	30.71	1.10	0.353	3	36.09	2.71	0.049
ERROR	76	27.82			98	13.33		

(a) DF = degrees of freedom
(b) MS = mean square

TABLE N2. WHITE BLOOD CELLS IN RATS: DESCRIPTIVE STATISTICS

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
0 MONTHS (GROUP C)							
0	8.05	0.54	10	0	8.74	0.55	10
50	(a) 6.03	0.34	10	25	(a) 6.25	0.32	10
100	8.53	0.63	10	50	7.97	0.48	10
200	7.59	0.48	10	100	7.70	0.39	10
3 MONTHS (GROUP C)							
0	8.77	0.29	10	0	7.17	0.37	10
50	(b) 7.04	0.36	9	25	(b) 5.79	0.22	10
100	(a) 5.77	0.19	10	50	(a) 5.35	0.17	10
200	(a) 6.15	0.24	10	100	(a) 5.01	0.20	9
6 MONTHS (GROUP C)							
0	7.30	0.43	6	0	5.34	0.27	10
50	(a) 5.40	0.38	4	25	(b) 4.53	0.24	10
100	(a) 4.40	0.14	9	50	(b) 4.57	0.17	10
200	(a) 3.42	0.14	8	100	(b) 4.46	0.35	9
9 MONTHS (GROUP C)							
0	6.00	0.36	9	0	4.37	0.36	7
50	(a) 3.76	0.15	7	25	(b) 3.42	0.28	6
100	(a) 2.86	0.22	7	50	(a) 3.29	0.13	10
200	(a) 3.63	0.41	9	100	(a) 2.67	0.18	8
12 MONTHS (GROUP C)							
0	5.30	0.67	6	0	2.29	0.28	8
50	(a) 2.70	0.26	6	25	(b) 1.53	0.08	6
100	(a) 2.56	0.37	7	50	(a) 1.26	0.09	9
200	(a) 2.62	0.28	6	100	(a) 1.39	0.08	8
12 MONTHS (GROUP B)							
0	8.12	0.90	5	0	3.44	0.25	9
50	(a) 5.01	0.29	8	25	3.56	0.33	9
100	(a) 4.20	0.31	7	50	3.09	0.17	8
200	(a) 2.97	0.10	8	100	2.71	0.24	8

TABLE N2. WHITE BLOOD CELLS IN RATS: DESCRIPTIVE STATISTICS (Continued)

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
15 MONTHS (GROUP B)							
0	7.04	0.59	5	0	3.20	0.12	10
50	(a) 4.25	0.27	8	25	3.07	0.33	10
100	(a) 4.04	0.17	9	50	3.19	0.13	9
200	(a) 3.37	0.50	7	100	3.51	0.22	9
18 MONTHS (GROUP B)							
0	5.17	0.63	6	0	3.72	0.19	10
50	(a) 3.54	0.19	7	25	3.00	0.30	9
100	(a) 3.40	0.20	8	50	3.28	0.61	9
200	(a) 2.80	0.32	7	100	2.89	0.27	9
21 MONTHS (GROUP B)							
0	5.76	0.65	5	0	4.16	0.33	10
50	(a) 3.56	0.10	5	25	3.27	0.18	8
100	(b) 4.30	0.70	4	50	4.08	1.07	9
200	5.80	0.87	4	100	(a) 2.82	0.08	9
24 MONTHS (GROUP B)							
0	4.47	0.35	4	0	2.69	0.26	9
50	4.80	0.54	6	25	3.87	0.72	8
100	4.85	0.75	2	50	3.33	0.94	6
200	5.55	0.95	2	100	2.70	0.51	4
24 MONTHS (GROUP A)							
0	5.39	0.81	28	0	3.40	0.30	32
50	6.34	1.58	21	25	2.72	0.20	27
100	5.41	0.77	21	50	3.27	0.32	24
200	8.69	1.90	10	100	5.69	1.82	19

(a) = Significantly different from control group mean (P = 0.01)
(b) = Significantly different from control group mean (P = 0.05)

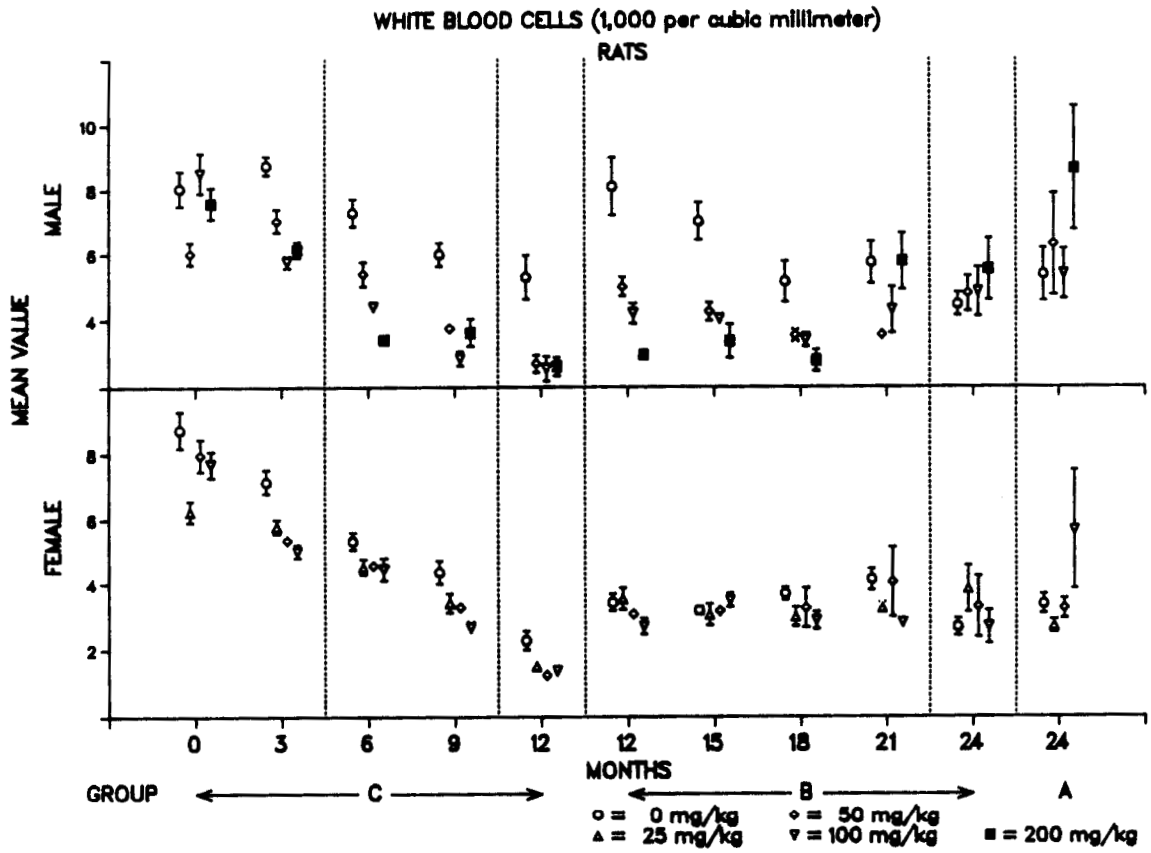


FIGURE 11. RESULTS OF WHITE BLOOD CELL COUNTS IN RATS IN THE TWELVE- AND TWENTY-FOUR-MONTH GAVAGE STUDIES OF BENZENE

TABLE N3. LYMPHOCYTES IN RATS: ANALYSES OF VARIANCE

SOURCE	MALE DF (a)	MALE MS (b)	MALE F	MALE PROB>F	FEMALE DF (a)	FEMALE MS (b)	FEMALE F	FEMALE PROB>F
0-3 MONTHS (GROUP C)								
DOSE	3	12.74	8.21	<0.001	3	11.38	11.70	<0.001
ANIMAL (DOSE)	36	1.55			36	0.97		
TIME	1	26.71	12.64	0.001	1	64.87	73.70	<0.001
DOSETIME	3	11.26	5.33	0.004	3	5.26	5.97	0.002
ERROR	35	2.11			35	0.88		
6-9 MONTHS (GROUP C)								
DOSE	3	16.83	41.40	<0.001	3	2.64	4.69	0.007
ANIMAL (DOSE)	32	0.41			35	0.56		
TIME	1	18.26	64.34	<0.001	1	20.01	66.75	<0.001
DOSETIME	3	1.42	5.01	0.010	3.	0.16	0.52	0.674
ERROR	19	0.28			27	0.30		
12 MONTHS (GROUP C)								
DOSE	3	7.03	19.23	<0.001	3	1.17	9.92	<0.001
ERROR	21	0.37			27	0.12		
12-21 MONTHS (GROUP B)								
DOSE	3	28.31	85.09	<0.001	3	4.40	11.58	<0.001
ANIMAL (DOSE)	30	0.33			35	0.38		
TIME	3	11.57	47.29	<0.001	3	3.39	14.03	<0.001
DOSETIME	9	1.94	7.93	<0.001	9	0.56	2.34	0.020
ERROR	57	0.24			94	0.24		
24 MONTHS (GROUP B)								
DOSE	3	0.99	7.81	0.006	3	0.25	0.82	0.494
ERROR	10	0.13			23	0.30		
24 MONTHS (GROUP A)								
DOSE	3	5.34	0.77	0.517	3	2.81	1.24	0.298
ERROR	76	6.93			97	2.26		

(a) DF = degrees of freedom
(b) MS = mean square

TABLE N4. LYMPHOCYTES IN RATS: DESCRIPTIVE STATISTICS

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
0 MONTHS (GROUP C)							
0	6.71	0.47	10	0	7.44	0.39	10
50	5.13	0.29	10	25	(b) 5.29	0.27	10
100	7.28	0.58	10	50	6.96	0.43	10
200	6.46	0.35	10	100	6.49	0.28	10
3 MONTHS (GROUP C)							
0	7.08	0.37	10	0	5.99	0.38	10
50	(a) 5.05	0.67	9	25	(a) 4.76	0.23	10
100	(b) 4.60	0.17	10	50	(b) 4.19	0.14	10
200	(b) 4.23	0.41	10	100	(b) 3.96	0.17	9
6 MONTHS (GROUP C)							
0	5.68	0.34	6	0	4.23	0.29	10
50	(b) 4.15	0.25	4	25	3.64	0.20	10
100	(b) 3.31	0.12	9	50	3.78	0.18	10
200	(b) 2.43	0.12	8	100	(b) 3.17	0.24	9
9 MONTHS (GROUP C)							
0	4.14	0.29	9	0	3.30	0.38	7
50	(b) 2.29	0.13	7	25	(a) 2.47	0.21	6
100	(b) 1.70	0.13	7	50	(b) 2.41	0.10	10
200	(b) 2.08	0.27	9	100	(b) 2.04	0.14	8
12 MONTHS (GROUP C)							
0	3.29	0.43	6	0	1.56	0.20	8
50	(b) 1.26	0.15	6	25	(a) 0.99	0.08	6
100	(b) 1.08	0.14	7	50	(b) 0.77	0.07	9
200	(b) 1.10	0.13	6	100	(b) 0.76	0.09	8

TABLE N4. LYMPHOCYTES IN RATS: DESCRIPTIVE STATISTICS (Continued)

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
12 MONTHS (GROUP B)							
0	6.12	0.62	5	0	2.76	0.24	9
50	(b) 3.18	0.22	8	25	(a) 2.19	0.24	9
100	(b) 2.43	0.24	7	50	(a) 2.17	0.14	8
200	(b) 1.44	0.08	8	100	(b) 1.94	0.19	8
15 MONTHS (GROUP B)							
0	4.48	0.15	5	0	2.29	0.13	10
50	(b) 2.46	0.16	8	25	(a) 1.73	0.18	10
100	(b) 2.09	0.16	9	50	2.03	0.16	9
200	(b) 1.66	0.22	7	100	2.32	0.20	9
18 MONTHS (GROUP B)							
0	2.71	0.26	6	0	2.35	0.11	10
50	(b) 1.68	0.10	7	25	(b) 1.44	0.08	9
100	(b) 1.58	0.10	8	50	(b) 1.45	0.23	9
200	(b) 1.07	0.11	7	100	(b) 1.29	0.08	9
21 MONTHS (GROUP B)							
0	2.99	0.19	5	0	2.36	0.22	10
50	(b) 1.68	0.10	5	25	(b) 1.46	0.05	8
100	(b) 1.68	0.10	4	50	(b) 1.59	0.26	9
200	(b) 1.29	0.22	4	100	(b) 1.23	0.08	9
24 MONTHS (GROUP B)							
0	2.34	0.25	4	0	1.27	0.11	9
50	2.06	0.10	6	25	1.68	0.23	8
100	1.52	0.21	2	50	1.41	0.25	6
200	(b) 0.96	0.24	2	100	1.40	0.33	4
24 MONTHS (GROUP A)							
0	2.93	0.63	28	0	1.83	0.17	32
50	1.82	0.25	21	25	1.22	0.15	27
100	2.26	0.66	21	50	1.35	0.23	24
200	2.11	0.38	10	100	1.88	0.69	18

(a) = Significantly different from control group mean (P = 0.05)
(b) = Significantly different from control group mean (P = 0.01)

B. White Blood Cells--Mice

For the first 9 months of study, the analyses of variance (Table N5) suggest systematic dose-related variation in WBC's (dose effect, $P<0.001$). Table N6 and Figure 12 give evidence of the compound-induced depression in WBC's in males during this period. The analysis of variance for Group B males in months 12-21 (Table N5) suggests strong dose effects that vary across time (dose effect, $P<0.001$; interaction, $P<0.001$). The significant dose $\times$ time interaction ($P<0.001$) reflects the shift in the relationship of high dose and vehicle control group means between months 18 and 21. With the exception of month 12, however, Group C high dose males exhibit depressed levels of WBC's from month 3 through month 18, giving strong evidence of compound-related reductions in numbers of WBC's. The data for females are more inconsistent than those of males and give less evidence of the compound-related response because of extremely variable patterns of response in adjacent measurement periods. Analysis specific to lymphocytes is presented in Tables N7 and N8.

TABLE N5. WHITE BLOOD CELLS IN MICE: ANALYSES OF VARIANCE

	MALE				FEMALE			
SOURCE	DF (a)	MS (b)	F	PROB>F	DF (a)	MS (b)	F	PROB>F
0-3 MONTHS (GROUP C)								
DOSE	3	8.66	5.47	0.003	3	4.42	2.09	0.119
ANIMAL (DOSE)	36	1.58			36	2.12		
TIME	1	0.39	0.31	0.581	1	31.13	12.32	0.001
DOSETIME	3	0.89	0.71	0.557	3	13.81	5.46	0.003
ERROR	26	1.27			36	2.53		
6-9 MONTHS (GROUP C)								
DOSE	3	56.58	10.90	<0.001	3	5.35	1.10	0.364
ANIMAL (DOSE)	34	5.19			35	4.88		
TIME	1	3.62	1.08	0.308	1	3.12	0.55	0.466
DOSETIME	3	0.99	0.30	0.829	3	8.41	1.47	0.243
ERROR	29	3.36			28	5.71		
12 MONTHS (GROUP C)								
DOSE	3	2.11	1.14	0.347	3	1.59	0.34	0.799
ERROR	34	1.85			32	4.72		
12-21 MONTHS (GROUP B)								
DOSE	3	44.16	6.75	0.001	3	18.41	9.24	<0.001
ANIMAL (DOSE)	36	6.55			36	1.99		
TIME	3	99.34	17.05	<0.001	3	0.54	0.46	0.717
DOSETIME	9	37.59	6.45	<0.001	9	5.41	4.54	<0.001
ERROR	92	5.82			96	1.19		
24 MONTHS (GROUP B)								
DOSE	2	17.30	2.35	0.141	3	4.75	2.23	0.120
ERROR	11	7.36			18	2.13		
24 MONTHS (GROUP A)								
DOSE	3	189.93	3.75	0.016	3	6.31	0.66	0.585
ERROR	51	50.65			67	9.61		

(a) DF = degrees of freedom
(b) MS = mean square

TABLE N6. WHITE BLOOD CELLS IN MICE: DESCRIPTIVE STATISTICS

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
0 MONTHS (GROUP C)							
0	6.02	0.19	10	0	4.91	0.34	10
25	5.74	0.63	10	25	6.30	0.79	10
50	(a) 4.66	0.31	10	50	4.67	0.31	10
100	5.31	0.43	10	100	(a) 7.00	0.68	10
3 MONTHS (GROUP C)							
0	6.22	0.25	6	0	5.25	0.50	10
25	5.93	0.39	9	25	4.87	0.19	10
50	(b) 3.96	0.18	7	50	4.26	0.40	10
100	(a) 4.62	0.45	8	100	3.51	0.34	10
6 MONTHS (GROUP C)							
0	10.33	1.16	9	0	4.96	0.36	10
25	(b) 7.62	0.38	10	25	6.34	0.79	10
50	(b) 5.82	0.56	8	50	(a) 7.96	1.56	9
100	(b) 6.72	0.49	10	100	5.38	0.46	10
9 MONTHS (GROUP C)							
0	9.75	1.15	8	0	5.69	0.40	9
25	7.68	0.52	10	25	6.20	0.52	7
50	(b) 5.54	0.46	7	50	5.89	0.35	7
100	(b) 5.89	0.49	9	100	5.93	0.76	9
12 MONTHS (GROUP C)							
0	5.13	0.41	9	0	5.40	0.42	10
25	5.10	0.61	10	25	5.66	0.84	10
50	4.17	0.25	10	50	5.00	0.77	6
100	4.53	0.41	9	100	4.75	0.77	10

TABLE N6. WHITE BLOOD CELLS IN MICE: DESCRIPTIVE STATISTICS (Continued)

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
12 MONTHS (GROUP B)							
0	7.08	0.51	10	0	6.48	0.34	10
25	4.74	0.33	10	25	(b) 4.12	0.32	10
50	5.56	0.38	10	50	(b) 3.20	0.23	10
100	(a) 4.00	0.31	10	100	(b) 2.94	0.14	10
15 MONTHS (GROUP B)							
0	7.65	0.54	10	0	4.46	0.34	10
25	6.16	0.79	10	25	4.22	0.28	10
50	6.70	0.50	9	50	3.34	0.24	10
100	(a) 5.02	0.65	10	100	4.10	0.33	10
18 MONTHS (GROUP B)							
0	9.76	0.52	10	0	5.51	0.36	10
25	7.91	0.79	10	25	(b) 3.73	0.42	9
50	(b) 5.63	0.52	6	50	(b) 3.98	0.36	9
100	(b) 5.76	1.20	10	100	(b) 3.81	0.80	9
21 MONTHS (GROUP B)							
0	10.00	1.05	9	0	4.38	0.22	9
25	(a) 6.51	0.63	7	25	4.17	0.46	7
50	(a) 6.67	0.75	6	50	3.67	0.31	8
100	(b) 14.49	2.42	7	100	4.57	0.84	7
24 MONTHS (GROUP B)							
0	4.52	1.07	5	0	4.40	0.61	8
25	8.03	1.39	6	25	4.53	0.54	6
50	7.07	0.13	3	50	2.52	0.30	5
100	--	--	0	100	3.57	1.07	3
24 MONTHS (GROUP A)							
0	7.93	1.27	22	0	3.87	0.55	22
25	8.41	1.46	15	25	4.64	0.56	19
50	(b) 15.60	2.30	13	50	4.22	0.76	19
100	12.64	5.32	5	100	5.40	1.35	11

(a) = Significantly different from control group mean (P = 0.05)
(b) = Significantly different from control group mean (P = 0.01)

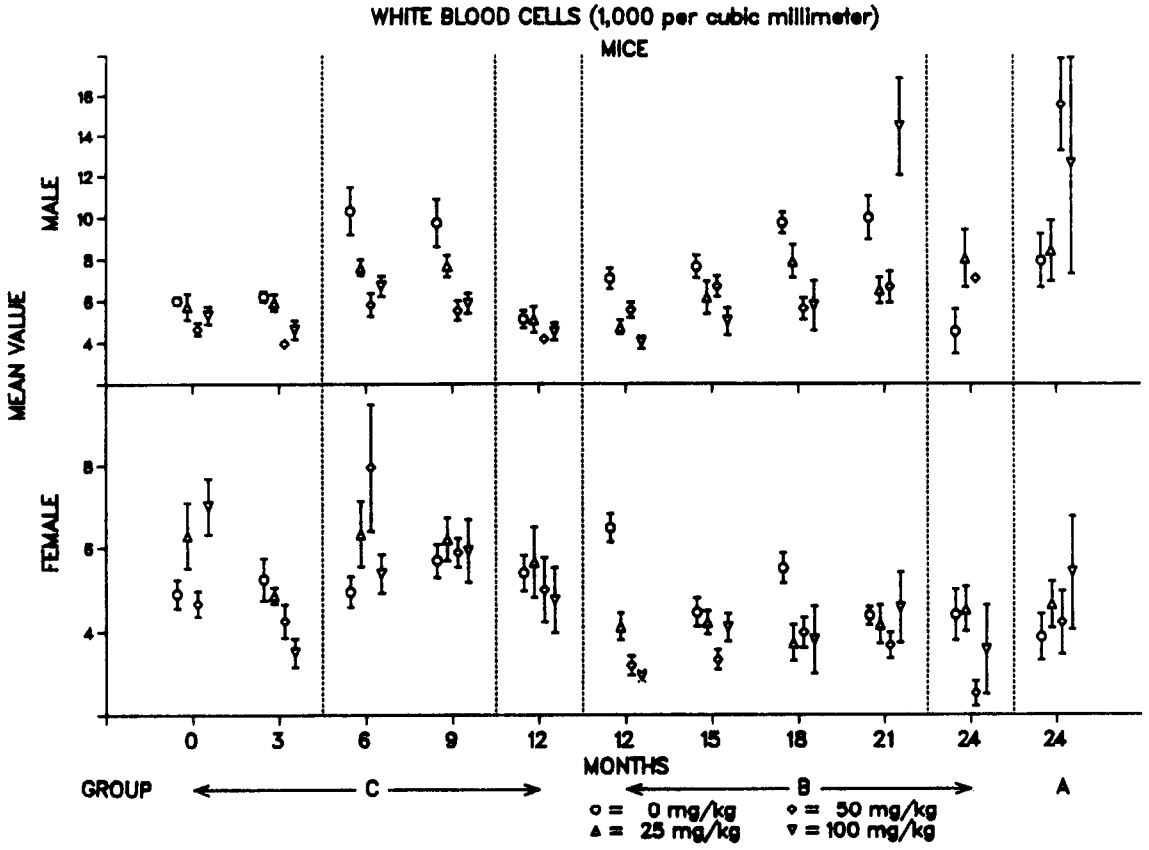


FIGURE 12. RESULTS OF WHITE BLOOD CELL COUNTS IN MICE IN THE TWELVE- AND TWENTY-FOUR-MONTH GAVAGE STUDIES OF BENZENE

TABLE N7. LYMPHOCYTES IN MICE: ANALYSES OF VARIANCE

SOURCE	MALE DF (a)	MALE MS (b)	MALE F	MALE PROB>F	FEMALE DF (a)	FEMALE MS (b)	FEMALE F	FEMALE PROB>F
0-3 MONTHS (GROUP C)								
DOSE	3	7.88	5.68	0.003	3	3.75	2.54	0.071
ANIMAL (DOSE)	36	1.39			36	1.48		
TIME	1	5.95	6.46	0.017	1	71.69	43.46	<0.001
DOSETIME	3	1.27	1.38	0.271	3	11.12	6.74	0.001
ERROR	26	0.92			36	1.65		
6-9 MONTHS (GROUP C)								
DOSE	3	33.93	14.52	<0.001	3	4.62	1.54	0.220
ANIMAL (DOSE)	34	2.34			35	2.99		
TIME	1	4.77	2.04	0.164	1	4.16	1.19	0.284
DOSETIME	3	0.20	0.08	0.968	3	5.63	1.62	0.207
ERROR	29	2.34			28	3.48		
12 MONTHS (GROUP C)								
DOSE	3	0.76	0.50	0.683	3	2.40	0.58	0.633
ERROR	34	1.50			32	4.15		
12-21 MONTHS (GROUP B)								
DOSE	3	72.38	26.34	<0.001	3	20.90	20.11	<0.001
ANIMAL (DOSE)	36	2.75			36	1.04		
TIME	3	2.45	1.70	0.170	3	2.32	3.12	0.029
DOSETIME	9	3.92	2.72	0.007	9	3.77	5.07	<0.001
ERROR	92	1.44			96	0.74		
24 MONTHS (GROUP B)								
DOSE	2	2.50	1.18	0.343	3	3.32	2.39	0.103
ERROR	11	2.12			18	1.39		
24 MONTHS (GROUP A)								
DOSE	3	6.17	2.67	0.056	3	4.27	1.29	0.285
ERROR	51	2.31			67	3.31		

(a) DF = degrees of freedom
(b) MS = mean square

TABLE N8. LYMPHOCYTES IN MICE: DESCRIPTIVE STATISTICS

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
0 MONTHS (GROUP C)							
0	5.08	0.22	10	0	4.36	0.37	10
25	4.25	0.58	10	25	5.64	0.71	10
50	(a) 3.95	0.31	10	50	4.16	0.28	10
100	(b) 3.53	0.33	10	100	(b) 6.27	0.57	10
3 MONTHS (GROUP C)							
0	4.35	0.32	6	0	3.93	0.34	10
25	4.53	0.43	9	25	3.57	0.15	10
50	(b) 2.50	0.16	7	50	2.99	0.12	10
100	(a) 2.71	0.25	8	100	(a) 2.38	0.22	10
6 MONTHS (GROUP C)							
0	6.67	0.59	9	0	3.89	0.28	10
25	5.77	0.38	10	25	5.19	0.76	10
50	(b) 3.89	0.48	8	50	(a) 6.27	1.12	9
100	(b) 3.85	0.28	10	100	3.95	0.36	10
9 MONTHS (GROUP C)							
0	6.58	0.95	8	0	4.46	0.31	9
25	5.03	0.55	10	25	4.75	0.47	7
50	(b) 3.59	0.15	7	50	4.47	0.31	7
100	(b) 3.14	0.39	9	100	4.25	0.54	9
12 MONTHS (GROUP C)							
0	3.07	0.35	9	0	3.16	0.39	10
25	3.38	0.62	10	25	3.50	0.76	10
50	3.02	0.21	10	50	3.92	0.70	6
100	2.69	0.22	9	100	4.30	0.76	10

TABLE N8. LYMPHOCYTES IN MICE: DESCRIPTIVE STATISTICS (Continued)

MALE				FEMALE			
DOSE (mg/kg)	MEAN	STANDARD ERROR	N	DOSE (mg/kg)	MEAN	STANDARD ERROR	N
12 MONTHS (GROUP B)							
0	5.17	0.40	10	0	4.82	0.52	10
25	(b) 3.00	0.23	10	25	(b) 3.00	0.25	10
50	(b) 3.21	0.23	10	50	(b) 2.00	0.15	10
100	(b) 2.44	0.25	10	100	(b) 1.51	0.08	10
15 MONTHS (GROUP B)							
0	5.11	0.21	10	0	3.79	0.31	10
25	4.35	0.68	10	25	2.92	0.22	10
50	(a) 3.68	0.53	9	50	(b) 2.06	0.20	10
100	(b) 2.41	0.33	10	100	3.41	0.30	10
18 MONTHS (GROUP B)							
0	6.27	0.36	10	0	3.71	0.35	10
25	5.47	0.81	10	25	(b) 2.51	0.36	9
50	(b) 2.93	0.31	6	50	(a) 2.61	0.26	9
100	(b) 2.00	0.29	10	110	(b) 1.79	0.23	9
21 MONTHS (GROUP B)							
0	5.51	0.59	9	0	2.98	0.24	9
25	4.47	0.57	7	25	2.27	0.29	7
50	(b) 3.03	0.29	6	50	2.29	0.28	8
100	(b) 2.55	0.27	7	100	2.25	0.48	7
24 MONTHS (GROUP B)							
0	2.65	0.59	5	0	3.03	0.39	8
25	3.80	0.71	6	25	3.10	0.54	6
50	2.50	0.45	3	50	1.44	0.12	5
100	--	--	0	100	2.34	1.14	3
24 MONTHS (GROUP A)							
0	3.31	0.29	22	0	2.60	0.51	22
25	3.73	0.44	15	25	3.19	0.41	19
50	3.69	0.48	13	50	2.24	0.29	19
100	1.63	0.31	5	100	2.01	0.38	11

(a) = Significantly different from control group mean (P=0.05)
(b) = Significantly different from control group mean (P=0.01)

II. Pathology Working Group Review of Benzene Hematology Data

A. Introduction

A Pathology Working Group review of the 2-year rat and mouse benzene hematology data took place on May 2, 1984, from 8:30 a.m. to 3:00 p.m. at NIEHS, Research Triangle Park, North Carolina. Statistically analyzed data as well as selected individual animal data were reviewed by the group. Consensus opinions on the quality and interpretation of the data were reached. Attention was focused on the total leukocyte count and lymphocyte count data and on erythroid parameters. No attention was given to percent differential or percent reticulocyte counts, since these are intermediary values used to calculate absolute counts. RBC count, hemoglobin, and MCV data were closely examined; hematocrit was given less attention, since it is a calculated value (not directly measured by the instrumentation used).

Three groups of rats and mice were designated for hematologic assessment in the study:

Group A: Forty animals of each species, sex, and dose group terminally bled at the 24-month kill

Group B: Ten animals of each species, sex, and dose group bled orbitally at 12, 15, 18, and 21 months and bled terminally at 24 months

Group C: Ten animals of each species, sex, and dose group bled orbitally at 0 (before dosing), 3, 6, and 9 months and bled terminally at 12 months

Orbital bleeding was without anesthesia, and terminal bleeding was by cardiac puncture under pentobarbital anesthesia.

B. Data Groupings

Since a number of important elements were not constant throughout the study, it was the opinion of the review group that looking at data trends over time was not justifiable except for short specific time intervals. In some instances, when two or three successive bleeding intervals did have most variables constant, the vehicle control animal hematology values for one or more intervals were unreasonable, making biologic interpretations difficult, if not impossible. Study elements (variables) that directly affected the quality and interpretability of the hematology data were:

1. Different method of bleeding at interim and final kill time points

Terminal bleedings were by cardiac puncture under barbiturate anesthesia, and interim bleedings were retro-orbital without anesthesia.

2. Different instrumentation for hematologic measurements

A Coulter Counter Model FN was used for the 0- and 3-month time point, and an Ortho ELT-8 was used for all remaining bleeding intervals. There is no documentation indicating that these instruments were calibrated such that results over time could be compared.

3. Different intervals between cessation of dosing and drawing of blood samples for hematologic analysis

Interim bleedings were obtained within 24 hours of the last dosing, and terminal bleedings obtained at kill did not follow this pattern in most instances. The 24-month terminal bleeding was at least 1 week after dosing ended. The 12-month terminal bleeding was 3 days after final dosing for male rats and 24 hours after final dosing for female rats and for mice of both sexes.

C. Comments on Specific Bleeding Intervals

0-Month (Group C): Measurements made with Coulter Counter Model FN

Significant differences between groups for some of the measurements raise concern regarding the method of sampling or analysis. The 0-month data were inconsistent and could not be evaluated.

3-Month (Group C): Measurements made with Coulter Counter Model FN

This grouping should be considered separately. It should not be used with subsequent data, since all subsequent data were obtained with a different instrument.

6- and 9-Month (Group C): Measurements made with ELT-8

Animals bled 24 hours after previous dose.

These groupings can be considered together in assessing time course effects of dosing.

12-Month (Group C): Measurements made with ELT-8

This was a terminal bleed with samples collected by cardiac puncture under barbiturate anesthesia. The bleeding occurred 3 days after last dose for male rats and 24 hours after last dose for female rats and mice of either sex.

This grouping must be considered as a unique data set.

12-Month (Group B): Measurements made with ELT-8

This was an orbital bleed 24 hours after last dose.

This data set may be considered along with the 15-, 18-, and 21-month data for determining time course effects.

15-, 18-, and 21-Month (Group B): Measurements made with ELT-8

Some of these data may be used in assessing time course effects. Atypically high control values for RBC counts were recorded for mice.

24-Month (Group B and Group C): Measurements made with ELT-8

Cardiac bleeding under barbiturate anesthesia. Bleeding occurred 1 week after last dose. Although these groups could be considered together, data variability, possibly related to intercurrent spontaneous disease, will preclude many potential conclusions.

D. Leukocyte Count

There is an apparent leukopenia in male rats in the early part of the 2-year study with a swing back toward control values at the 21-month bleeding interval. In female rats, there was a compound-related leukopenia evident between the 3rd and 12th months of dosing.

During examination of mouse WBC data, it was noted that the male vehicle control group means at 6 and 9 months were high, giving a possible false impression of a compound-related leukopenia at these intervals. Similarly, high vehicle control group values were noted in males at 18 and 21 months. The compound-associated leukopenia in females at 12 and 18 months seems real and lends support to the possibility that something similar is happening in males at the same intervals.

The presence of potential outlier WBC values at 21 months in males was discussed. Some statistical editing is in order.

E. Lymphocyte Count

The peer review group consensus was that dose-related lymphocytopenia in male rats was evident from 3 to 21 months. A similar but less dramatic effect is present in females. Because there are potential problems with how data were obtained (see previous concerns), it was stated that these data are in part believable because they support an already existing body of literature that is sound.

A question was raised regarding the male control rat sample size starting at 12 months (Group B). There are only 5 or 6 rat samples instead of the anticipated 10. Some explanation for this shortage in number of vehicle control animals should be provided.

Since the 24-month bleeding interval followed cessation of dosing by 1 week, it was the group consensus that the effects of benzene on leukocyte counts could not be assessed at this interval. This consensus is predicated on the short resident time of leukocytes in the peripheral circulation.

In male mice, lymphocytopenia was evident at 3 through 9 months in Group C and 12 through 21 months in Group B. In female mice, lymphocytopenia was evident between 12 and 18 months.

F. RBC Count, Hemoglobin, and MCV

No compound-associated changes in RBC count were evident in male or female rats at any sampling interval during the study. Mouse RBC and related data cannot be interpreted because of the unusually high vehicle control group values at several sampling intervals. Some of the individual mouse RBC values at these intervals are nonphysiologic.

Findings for hemoglobin determinations are essentially similar to those for RBC counts with no apparent compound-associated changes in rats and with data that cannot be interpreted in mice.

MCV data show too much variability to permit interpretation for either rats or mice.

III. Conclusions

Any interpretation of the benzene hematology data should be made with a great deal of caution, since several parameters changed during the course of the studies and in several instances atypical vehicle control group values were obtained. Although study of individual hematology ticket data from the analyzer indicates that the ELT-8 was functioning properly, there is a high suspicion that sample collection and possibly sample handling were less than optimal. Because of the above reservations, little could be definitely concluded with respect to the large amount of hematology data that were generated. Reliably identifiable hematologic effects were limited to lymphocytopenia and associated leukocytopenia in rats and mice administered benzene. Attempts to correlate hematologic changes with anatomic pathology changes would be inappropriate, since the technical quality of the hematology data was questionable.

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

The available records, experimental data, pathology materials, and the draft Technical Report of these studies were examined for overall correspondence and for Good Laboratory Practice compliance and scientific procedures. The audit was conducted during the period August 29 through September 2, 1983. The following persons were involved in the audit: National Toxicology Program--Dr. M. Wolfe, pathologist; Dr. B. Gupta, pathologist; Dr. C. Lingeman, pathologist; Ms. A. Grant, histotechnician; Dr. J. Huff, chemical manager, toxicologist; Ms. C. Davies, chemist; Dr. C. Whitmire, quality assurance; Dr. R. Maronpot, clinical pathologist; and Dr. B. Schwetz, toxicologist, audit team leader; Experimental Pathology Laboratories--Dr. W. Busey, pathologist; and Ms. H. Cooke, histotechnician; Tracor Jitco, Inc.--Ms. P. Errico, data specialist.

The full report of the NTP audit of the benzene data file and the report of a site visit to the Battelle Columbus Laboratories are on file at the National Toxicology Program, NIEHS. The following were the main findings and their resolutions:

1. *Preparation of dosing solutions*--The daily administration of benzene to the animals was documented, but no data were found that identified the procedures for the weekly preparation of dosing solutions. The data indicated which dose volumes were used for each group of rats or mice at various intervals but not how the dosing solutions were prepared. Because daily notations were made regarding dose and dose response, however, the fact that data on dose preparation procedures were missing is not considered to be a significant deficiency in these studies.

2. *Determination of cause of death*--Some animal deaths that were identified as gavage-related based on histologic findings were not coded as accidental deaths. These discrepancies were distributed among groups of mice and rats in such a way as to not significantly influence the interpretation of data. This discrepancy was corrected in the data, and the final interpretation of the study takes into account the corrections.

3. *Hematology data*--Hematology data were not positively identified by individual animal or study. Blood count data were printed out on "tickets" from an automated analyzer without unique animal or study identification, one ticket per animal. The data then were transcribed to data sheets and identified by unique animal numbers. Communication with personnel from the laboratory subsequent to the audit confirmed that laboratory numbers (ticket numbers) were never repeated on a given day's run. Since the final decision regarding benzene's carcinogenic potential is not dependent on these data and since there is no indication in the data set that there was any mixup of these hematologic values, the fact that individual animal identification is not available is not considered to be a major limitation in the use of these data.

4. *Animal identification*--Carcasses and wet tissues in formalin were not positively identified by dose level of benzene and, in some cases, were not identified by individual animal number. During the studies, ear punches were used to identify animals by benzene dose and toe clips were used to provide individual animal identification. At the time these studies was conducted, the NTP did not require that either the ears or the feet of animals be included with the wet tissues in formalin. During the audit, animal identification was checked against the label on the wet tissue bag. Eighty-six percent of the animals checked (79/92) were correctly identified, 13% (12/92) could not be identified because there were no feet in the bag of tissues, and one animal was incorrectly identified. In the absence of any indication elsewhere in the data that animals were misidentified or mixed up, animal identification was not considered to be a significant problem.

These findings and comments are based on the NTP audit of the raw data and communications with personnel from Battelle Columbus Laboratory, including a site visit after the audit was performed. Any discrepancies that might have significantly influenced the final interpretation of these studies in F344/N rats and $B6C3F_1$ mice were resolved. Minor problems not mentioned here which were not considered to affect the outcome of the studies were not necessarily pursued to final resolution but are identified in the NTP audit report. In conclusion, the data examined in this audit are considered adequate to meet the objectives and support the findings of these studies.

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-292:41053