NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

2-BUTOXYETHANOL

(CAS NO. 111-76-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

March 2000

NTP TR 484

NIH Publication No. 00-3974

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

FOREWORD

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

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

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

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

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

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CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

J.H. Roycroft, Ph.D., Study Scientist
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
L.T. Burka, Ph.D.
B.I. Ghanayem, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.R. Maronpot, D.V.M.
A. Nyska, D.V.M.
G.N. Rao, D.V.M., Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., Integrated Laboratory Systems

Battelle Pacific Northwest Laboratories
Conducted studies, evaluated pathology findings

B.J. Chou, D.V.M., Ph.D., Principal Investigator
J.A. Dill, Ph.D.
S.L. Grumbein, D.V.M., Ph.D
K.M. Lee, Ph.D.
R.A. Miller, D.V.M., Ph.D.
H.A. Ragan, D.V.M.
S.E. Rowe, D.V.M., M.S.
R.B. Westerberg, Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
E.T. Gaillard, D.V.M., M.S.
C.C. Shackelford, D.V.M., M.S., Ph.D.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on rats (14 October 1997)

M.P. Jokinen, D.V.M., Chairperson
Pathology Associates International
T. Amanuma, D.V.M., Observer
National Toxicology Program
R. Cattley, V.M.D., Ph.D.
Chemical Industry Institute of Toxicology
E.T. Gaillard, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
R.H. Garman, D.V.M., Observer
Canadian Medical Association
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.
National Toxicology Program
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (25 September 1997)

M.P. Jokinen, D.V.M., Chairperson
Pathology Associates International
R.H. Garman, D.V.M., Observer
Canadian Medical Association
J.E. Heath, D.V.M.
Southern Research Institute
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
J.R. Leininger, D.V.M., Ph.D.
National Toxicology Program
J. Mahler, D.V.M., Ph.D.
National Toxicology Program
R.A. Miller, D.V.M., Ph.D.
Battelle Pacific Northwest Laboratories
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
A. Singer, D.V.M.
Battelle Columbus Laboratories

Analytical Sciences, Inc.
Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
K.P. McGowan, M.B.A.
M.A. Mauney, M.S.
N.G. Mintz, B.S.
J.T. Scott, M.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
J.R. Carlton, B.A.
L.M. Harper, B.S.
T.S. Kumpe, M.A.
A.M. Macri-Hanson, M.A., M.F.A.
M.L. Rainer, B.S.

CONTENTS

ABSTRACT

CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-OH

2-BUTOXYETHANOL

CAS No. 111-76-2

Chemical Formula: $C_6H_{14}O_2$ Molecular Weight: 118.17

Synonyms: 2-Butoxy-1-ethanol; *m*-butyl ether; butyl glycol; ethylene glycol monobutyl ether
Trade name: Butyl Cellosolve

2-Butoxyethanol is a member of a family of ethylene glycol monoalkyl ethers. It is used extensively as a solvent in surface coatings such as lacquers, enamels, varnishes, and latex paint; in paint thinners, paint stripping formulations, and inks; and in degreasers and industrial and household cleaners. 2-Butoxyethanol was nominated for study because of its widespread use in industrial and consumer applications, the potential for exposure to workers and the general population, and the absence of chronic toxicity data. Male and female F344/N rats and B6C3F_1 mice were exposed to 2-butoxyethanol (greater than 99% pure) by inhalation (primary route of human exposure) for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and the bone marrow of male F344/N rats and B6C3F_1 mice.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 hours per day, 5 days per week for 14 weeks. One female rat in the 250 ppm group was killed moribund during week 8; four females in the 500 ppm group were killed moribund during week 1 and one during week 5. Final mean body weights of females exposed to 500 ppm were significantly less than those of the chamber controls. Clinical findings included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy, and increased salivation and/or lacrimation. Due to vascular thrombosis and infarction in the tail vertebrae of 500 ppm female rats, the tails became necrotic and either sloughed off or were chewed off. The primary effect on the hematopoietic system was an anemia characterized as macrocytic, normochromic, and regenerative in males exposed to 125 ppm or greater and, to a greater extent, in all exposed groups of females. Compared to the chamber controls, kidney weights of males exposed to 500 ppm and females exposed to 125 ppm or greater and liver weights of males exposed to 250 or 500 ppm and females exposed to 125 ppm or greater were significantly increased, and thymus weights of females exposed to 500 ppm were significantly less. In female rats killed moribund, there was considerable histologic evidence of thrombosis in tissues and organs including the nasal cavity, incisors, liver, lung, and heart. In addition to thrombosis, infarction occurred in the vertebrae of the tail resulting in necrosis and loss of the distal portion of the tail. There were also inflammation, necrosis, and ulceration of the forestomach; necrosis and centrilobular degeneration of the liver; renal tubule

degeneration; and atrophy of the spleen and thymus. Exposure-related increases in the incidences of Kupffer cell pigmentation, forestomach inflammation and epithelial hyperplasia, bone marrow hyperplasia, splenic hematopoietic cell proliferation, and renal tubule pigmentation were observed in male and/or female rats surviving to the end of the study.

14-Week Study in Mice

Groups of 10 male and 10 female mice were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm, 6 hours per day, 5 days per week for 14 weeks. Two male and two female mice exposed to 500 ppm died and two males and two females were killed moribund during the first 2 weeks of the study. Final mean body weights of 125, 250, and 500 ppm male mice were significantly less than those of the chamber controls. Clinical findings were observed only in 500 ppm males and females that died or were killed moribund and included abnormal breathing, red urine stains, and lethargy. Hematologic evaluation indicated an anemia that was characterized as normocytic, normochromic, and regenerative in mice exposed to 62.5 ppm or greater; the anemia was more pronounced in females. Liver weights of males exposed to 500 ppm were significantly greater than the chamber controls. In mice either dying early or killed moribund, there were inflammation, necrosis, and ulceration of the forestomach; mediastinal pleura and peritoneal inflammation associated with the forestomach lesions; liver necrosis; renal tubule degeneration; atrophy of the spleen, thymus, and mandibular and mesenteric lymph nodes; and degeneration of the testis. Exposure-related increases in the incidences of hematopoietic cell proliferation and hemosiderin pigmentation of the spleen, Kupffer cell hemosiderin pigmentation of the liver, inflammation and epithelial hyperplasia of the forestomach, and renal tubule hemosiderin pigmentation occurred in male and/or female mice surviving to the end of the study.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 31.2, 62.5, or 125 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 27 male and 27 female rats were exposed to 0, 62.5, or 125 ppm for evaluation at 3, 6, and 12 months and nine male and nine female rats were exposed to 31.2 ppm for evaluation at 3 (hematology only) and 6 months.

Survival and Body Weights

Survival of exposed male and female rats was similar to the chamber control groups. The mean body weights of females exposed to 125 ppm were generally less than the chamber control group.

Hematology and Bone Marrow Cellularity

The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related mild macrocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females more affected than males. Significant increases in bone marrow cellularity and decreases in the myeloid/erythroid ratio relative to the chamber controls were observed at all time points in females exposed to 125 ppm, and a decrease in the myeloid/erythroid ratio was observed in males exposed to 125 ppm at 12 months.

Pathology Findings

The incidence of benign or malignant pheochromocytoma (combined) of the adrenal medulla in females exposed to 125 ppm was not significantly increased compared to the chamber controls but exceeded the historical control range. Exposure-related increases in the incidences of hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation of the liver were observed in male and female rats.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to 2-butoxyethanol by inhalation at concentrations of 0, 62.5, 125, or 250 ppm, 6 hours per day, 5 days per week for 104 weeks. For hematology and bone marrow analyses, additional groups of 30 male and 30 female mice were exposed to 0, 62.5, 125, or 250 ppm for evaluation at 3, 6, and 12 months.

Survival and Body Weights

Survival of male mice exposed to 125 or 250 ppm was significantly less than that of the chamber control group. The mean body weights of exposed males

were generally less than those of the chamber control group during the last 6 months of the study. The mean body weights of exposed female mice were less than those of the chamber control group; the reductions were greater and occurred earlier than those observed in males.

Hematology

The most consistent exposure-related effect on the hematopoietic system was an exposure concentration-related minimal normocytic, normochromic, regenerative anemia present at 3, 6, and 12 months, with females affected slightly more than males.

Pathology Findings

In females exposed to 250 ppm, incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma (combined) were significantly increased relative to the chamber controls, and these incidences exceeded the ranges in historical chamber controls. In 2-butoxyethanol exposed males, there were possible exposure-related increases in the incidences of squamous cell papilloma of the forestomach, although the increases were not significant and the incidences were within the historical control range for chamber controls. Accompanying these neoplasms in females and, to a lesser extent, in males were exposure-related increases in the incidences of ulcer and epithelial hyperplasia of the forestomach.

In male mice exposed to 250 ppm, the incidence of hemangiosarcoma of the liver was significantly increased relative to chamber controls and exceeded the range in historical controls; in addition, there were possible exposure-related increases in the incidence of hepatocellular carcinoma. Incidences of hemosiderin pigmentation in the Kupffer cells were significantly increased in 125 and 250 ppm males and all exposed groups of females.

The incidences of splenic hematopoietic cell proliferation and hemosiderin pigmentation were generally increased in males and females, and the incidences of bone marrow hyperplasia were increased in males. The incidences of hyaline degeneration of the olfactory and respiratory epithelia of the nose were increased in female mice.

GENETIC TOXICOLOGY

2-Butoxyethanol did not induce mutations in any of the *S. typhimurium* strains tested, with or without induced hamster or rat liver S9. 2-Butoxyethanol induced cycle delay but did not induce either sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells with or without S9. 2-Butoxyethanol did not induce micronuclei in bone marrow cells of male rats or mice administered the chemical by intraperitoneal injection three times at 24-hour intervals.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of 2-butoxyethanol in male F344/N rats exposed to 31.2, 62.5, or 125 ppm. There was *equivocal evidence of carcinogenic activity* of 2-butoxyethanol in female F344/N rats based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in male B6C3F_1 mice based on increased incidences of hemangiosarcoma of the liver. A marginal increase in the incidences of forestomach squamous cell papilloma and an increase in the incidences of hepatocellular carcinoma may have been exposure related. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in female B6C3F_1 mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

Increased incidences of forestomach neoplasms in male and female mice occurred in groups in which ulceration and hyperplasia were also present.

Exposure to 2-butoxyethanol caused a mild regenerative anemia and effects secondary to the anemia.

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

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 31.2, 62.5, and 125 ppm	Chamber control, 62.5, 125, and 250 ppm	Chamber control, 62.5, 125, and 250 ppm
Body weights	Exposed groups similar to the chamber control group	125 ppm group less than the chamber control group	Exposed groups generally less than the chamber control group	Exposed groups less than the chamber control group
Survival rates	19/50, 11/50, 21/50, 24/50	29/50, 27/50, 23/50, 21/50	39/50, 39/50, 27/50, 26/50	29/50, 31/50, 33/50, 36/50
Nonneoplastic effects	Nose: olfactory epithelium, hyaline degeneration (13/48, 21/49, 23/49, 40/50) Liver: Kupffer cell pigmentation (23/50, 30/50, 34/50, 42/50)	Nose: olfactory epithelium, hyaline degeneration (13/50, 18/48, 28/50, 40/49) Liver: Kupffer cell pigmentation (15/50, 19/50, 36/50, 47/50)	Forestomach: ulcer (1/50, 2/50, 9/49, 3/48); epithelium hyperplasia (1/50, 7/50, 16/49, 21/48) Liver: Kupffer cell pigmentation (0/50, 0/50, 8/49, 30/49) Spleen: hematopoietic cell proliferation (12/50, 11/50, 26/48, 42/49); hemosiderin pigmentation (0/50, 6/50, 45/48, 44/49) Bone Marrow: hyperplasia (0/50, 1/50, 9/49, 5/50)	Forestomach: ulcer (1/50, 7/50, 13/49, 22/50); epithelium hyperplasia (6/50, 27/50, 42/49, 44/50) Liver: Kupffer cell pigmentation (0/50, 5/50, 25/49, 44/50) Spleen: hematopoietic cell proliferation (24/50, 29/50, 32/49, 35/50); hemosiderin pigmentation (39/50, 44/50, 46/49, 48/50) Nose: olfactory epithelium, hyaline degeneration (6/50, 14/50, 11/49, 12/50); respiratory epithelium, hyaline degeneration (17/50, 35/50, 26/49, 23/50)
Neoplastic effects	None	None	Liver: hemangiosarcoma (0/50, 1/50, 2/49, 4/49)	Forestomach: squamous cell papilloma (0/50, 1/50, 2/50, 5/50); squamous cell papilloma or carcinoma (0/50, 1/50, 2/50, 6/50)
Uncertain findings	None	Adrenal Medulla: benign or malignant pheochromocytoma (3/50, 4/50, 1/49, 8/49)	Forestomach: squamous cell papilloma (1/50, 1/50, 2/49, 2/49) Liver: hepatocellular carcinoma (10/50, 11/50, 16/49, 21/49)	None
Level of evidence of carcinogenic activity	No evidence	Equivocal evidence	Some evidence	Some evidence

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

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, TA1535, and TA1537, with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Micronucleated erythrocytes	
Rat bone marrow *in vivo*:	Negative
Mouse bone marrow *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on 2-butoxyethanol on 30 October 1998 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

Gary P. Carlson, Ph.D., Chairperson
School of Health Sciences
Purdue University
West Lafayette, IN

A. John Bailer, Ph.D.
Department of Mathematics and Statistics
Miami University
Oxford, OH

Steven A. Belinsky, Ph.D.
Inhalation Toxicology Research Institute
Kirkland Air Force Base
Albuquerque, NM

James S. Bus, Ph.D.
Health and Environmental Sciences
Dow Chemical Company
Midland, MI

Linda A. Chatman, D.V.M.*
Pfizer, Inc.
Groton, CT

John M. Cullen, V.M.D., Ph.D.
Department of Microbiology, Parasitology, and Pathology
College of Veterinary Medicine
North Carolina State University
Raleigh, NC

Susan M. Fischer, Ph.D.*
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

Thomas L. Goldsworthy, Ph.D.*
Integrated Laboratory Systems
Research Triangle Park, NC

Stephen S. Hecht, Ph.D.
University of Minnesota Cancer Centers
Minneapolis, MN

Michele Medinsky, Ph.D.
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Jose Russo, M.D.*
Fox Chase Cancer Center
Philadelphia, PA

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 30 October 1998 the draft Technical Report on the toxicology and carcinogenesis studies of 2-butoxyethanol received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.H. Roycroft, NIEHS, introduced the toxicology and carcinogenesis studies of 2-butoxyethanol by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on the survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. In addition to the standard core study, a number of animals were assessed for hematologic parameters and bone marrow cellularity and myeloid/erythroid ratios. Additionally, animals were included in the design for toxicokinetic measures of 2-butoxyethanol and its principal metabolite, 2-butoxyacetic acid. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *some evidence of carcinogenic activity* in male and female B3C6F$_1$ mice.

Dr. Medinsky, a principal reviewer, agreed in principle with the proposed conclusions. Her concern was that the proposed conclusions for female rats and male mice were made based on differences in response of the test animals compared with historical control values and were not based on differences in response compared to respective controls. She asked what objective statistical measure of differences was used. Dr. Roycroft responded that, as a rule, neoplasm data are not compared statistically with historical control data because so many factors can vary from study to study. The concurrent controls are still considered the most appropriate control group. Dr. J.K. Haseman, NIEHS, said that many factors, such as whether there were increases in incidences of preneoplastic lesions, factored into a decision. Dr. Medinsky commented that one of the report's strengths was the comprehensive section on the chemical disposition and toxicokinetics of 2-butoxyethanol and 2-butoxyacetic acid and suggested a summary paragraph for the chemical disposition and toxicokinetics data (pages 19-20).

Dr. Bailer, the second principal reviewer, agreed with the proposed conclusions for rats but not for mice. He thought that not enough consideration was given to the strong exposure-related trends in the neoplasm data in mice. He asked for clarification as to why the findings did not support a conclusion of *clear evidence* in mice. Dr. Roycroft said that benign and malignant neoplasms are analyzed independently and in combination, with the most important being the combined neoplasms. For male mice, the combined incidences of hepatocellular adenoma or carcinoma did not increase, and the incidences of carcinoma alone were within the historical control range. Dr. J.R. Hailey, NIEHS, noted that whether more emphasis is given to the combined neoplasm incidence depends somewhat on the neoplasm type. With liver neoplasms, there is a morphologic and biologic continuum of progression from foci to adenomas and to carcinomas. Further, it is often difficult to distinguish benign from malignant neoplasms.

Dr. Cullen, the third principal reviewer, agreed with the proposed conclusions. He said that, in the liver of male mice, reliance on historical control incidence and lack of concordant increases in preneoplastic and benign lesions supported less than *clear evidence*, but the data appeared to reflect at least *equivocal evidence*. In female mice, he found the proposed conclusion regarding squamous papillomas appropriate. Dr. Cullen commented that some of the toxic effects attributed directly to action of the chemical might be addressed as secondary responses due to other insults created by the chemical, e.g., anemia in response to blood loss from gastric ulceration in female, and perhaps male, mice.

Dr. T.R. Tyler, Chemical Manufacturers Association Ethylene Glycol Ethers Panel, stated that 2-butoxyethanol has long been recognized primarily as a hemolytic agent, with humans being less susceptible than rodents. Regarding the forestomach neoplasms in female mice, he thought that *some*

evidence was probably correct but likely irrelevant because there is no such organ in humans. Regarding the pheochromocytomas in female rats, he asked the Subcommittee to reconsider the designation of *equivocal evidence* as there were no statistically significant pairwise comparisons, the incidence was barelyoutside the historical control range, and there was no indication of increased incidences in males.

Dr. R. Boatman, Eastman Chemical Company, thought that hemangiosarcomas of the liver in male mice represented a marginal or equivocal finding. He compared the results for this study with those from the NTP bioassay of *p*-nitroaniline (NTP, 1993a), for which similar incidences of hemangiosarcomas of the liver in male mice were classified as equivocal evidence. Further, he stated that the possibility that the study was compromised by *Helicobacter* infection could not be ruled out. Dr. Medinsky asked for staff comment on the *p*-nitroaniline study. Dr. Roycroft responded that the *p*-nitroaniline study was a gavage study and that the historical control range and high incidence for gavage studies at the time were slightly higher than the range and high incidence for the current inhalation study of 2-butoxyethanol.

Dr. Medinsky moved that under the conditions of this study, the Technical Report on 2-butoxyethanol be accepted with revisions discussed and the conclusions as written. Dr. Bailer seconded the motion. Dr. Cullen asked whether a sentence could be added to the conclusion for male mice that there was an exposure-concentration related increase in the incidences of malignant hepatocellular neoplasms. Dr. Roycroft noted that the increased incidences of hepatocellular neoplasms in male mice could be added to the sentence about the marginal increases in the incidences of forestomach neoplasms. There was consensus that that addition would be acceptable. The motion was accepted with five yes votes with one abstention (Dr. Bus).

INTRODUCTION

CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-OH

2-BUTOXYETHANOL

CAS No. 111-76-2

Chemical Formula: $C_6H_{14}O_2$ Molecular Weight: 118.17

Synonyms: 2-Butoxy-1-ethanol; *m*-butyl ether; butyl glycol; ethylene glycol monobutyl ether
Trade name: Butyl Cellosolve

CHEMICAL AND PHYSICAL PROPERTIES

2-Butoxyethanol is a member of a family of ethylene glycol monoalkyl ethers. It has a melting point of –70° C, a boiling point of 171° C, a density of 0.9012 g/mL, and a vapor pressure of 0.88 mm Hg at 25° C. It is miscible with water and soluble in mineral oil and most organic solvents. Although considered combustible, 2-butoxyethanol does not ignite readily and has a flash point of 60° C (closed cup) and flammability limits of 1.13% to 10.6% (*Patty's*, 1994; *Merck Index*, 1996; HSDB, 1998).

PRODUCTION, USE, AND HUMAN EXPOSURE

2-Butoxyethanol is produced by reacting ethylene oxide with butyl alcohol. It may also be produced by reacting ethylene chlorohydrin or ethylene glycol with sodium hydroxide and dialkyl sulfide (HSDB, 1998). It is used extensively as a solvent in surface coatings such as lacquers, enamels, varnishes, and latex paint; in paint thinners, paint stripping formulations, and inks; and in degreasers and industrial and household cleaners (NIOSH, 1990; ATSDR, 1998; HSDB, 1998). It was estimated that in the United States in the 1970s, over 740 products contained 2-butoxyethanol at an average concentration of 2.8% (Vincent *et al.*, 1993). Over half of these products were used in the home. 2-Butoxyethanol concentrations in commercial products vary depending upon the product and its use. For example, 2-butoxyethanol may reach concentrations of 35% for paint strippers, 5% for paint thinners, 21% for window cleaners, and 0.4% for inks (Vincent *et al.*, 1993; ATSDR, 1998). As a coupling agent, it stabilizes immiscible ingredients in metal cleaning products, textile lubricants, cutting oils, and hydraulic fluids. It is also used as a chemical intermediate in the production of acetate esters as well as phthalate and stearate plasticizers (HSDB, 1998). 2-Butoxyethanol is the largest volume alkyl glycol ether produced, with an estimated 390 million pounds produced in the United States in 1992 (USITC, 1992).

Because of its large production volume and widespread use, workers involved in the manufacture and formulation of products as well as consumers are potentially exposed to 2-butoxyethanol. According to the National Occupational Exposure Survey (1981-1983), 1,680,768 workers were potentially exposed to 2-butoxyethanol annually (NIOSH, 1990). The time-weighted average threshold limit value for 2-butoxyethanol (skin notation) is 20 ppm (ACGIH,

1999). The exposure limit of 2-butoxyethanol permitted by the Occupational Safety and Health Administration is 50 ppm (also with a skin designation), while The National Institute for Occupational Safety and Health (NIOSH) recommends a 10-hour time-weighted average of 5 ppm or 24 mg/m^3 (also with a skin designation) (HSDB, 1998). NIOSH has estimated that most workplace exposures are below 7 ppm; however, 2-butoxyethanol concentrations ranged from 0.04 to 367 ppm in various industrial operations in Belgium (Veulemans *et al.*, 1987; NIOSH, 1990). 2-Butoxyethanol, because of its volatility and its solubility properties, enters the environment by air emissions, via leachate from municipal landfills and hazardous waste sites, and water runoff. 2-Butoxyethanol has been detected in drinking water from several major United States municipalities (concentrations not provided), groundwater (United States, 23 μg/L), surface water (Japan, 5.68 μg/L), and industrial wastewater (United States, less than 100 μg/L). According to the National Ambient Volatile Organic Compounds Database (Shah and Singh, 1988), the average daily home indoor air concentration of 2-butoxyethanol is 0.214 ppb (1.0 μg/m^3); however, concentrations as high as 8 μg/m^3 have been detected in homes in Italy. 2-Butoxyethanol has been measured in air from commercial buildings at 34 μg/m^3, in commercial building exhaust at 13 μg/m^3, and in elevator shafts at 19 μg/m^3 (ATSDR, 1998; HSDB, 1998).

ABSORPTION, DISTRIBUTION, METABOLISM, AND ELIMINATION

Experimental Animals

Carpenter *et al.* (1956) first demonstrated that 2-butoxyethanol was absorbed following short-term exposure of rats, rabbits, dogs, and guinea pigs to 100 to 400 ppm 2-butoxyethanol and of human volunteers to 100 to 200 ppm 2-butoxyethanol. 2-Butoxyacetic acid was excreted in the urine, with most being excreted within 24 hours. Since then, the toxicokinetics and metabolism of 2-butoxyethanol have been extensively studied in humans and in several other species (primarily the male rat and predominantly the male F344/N rat) by the inhalation, oral, dermal, and intravenous routes of administration. Comprehensive reviews of this work have been published (ATSDR, 1998; CIRP, 1996).

2-Butoxyethanol, like the other alkyl glycol ethers, 2-ethoxy- and 2-methoxyethanol, is readily absorbed from the lungs and gastrointestinal tract and through the skin, rapidly distributed into tissues, metabolized, and eliminated. The major route of metabolite elimination is urinary excretion, followed by exhalation of CO_2. 2-Butoxyethanol, as with 2-ethoxy- and 2-methoxyethanol, is oxidized in the rat liver by alcohol dehydrogenase (Johanson *et al.*, 1986a; Ghanayem *et al.*, 1987a) to an intermediate aldehyde (butoxyacetaldehyde) that then undergoes further oxidation by aldehyde dehydrogenase (Ghanayem *et al.*, 1987a) to the respective acid (2-butoxyacetic acid). A proposed metabolic scheme for 2-butoxyethanol (ATSDR, 1998) is shown in Figure 1. The pathways of 2-butoxyethanol metabolism, whether by oxidation, conjugation, or dealkylation, appear to be saturable, and the differences in metabolism noted for various routes of exposure may be due merely to differences in the internal dose achieved. In the male rat, 2-butoxyacetic acid is the major metabolite of 2-butoxyethanol, and its excretion in urine represents 60% to 75% of the absorbed dose of 2-butoxyethanol regardless of whether the route of administration is dermal (Sabourin *et al.*, 1992a), drinking water (Medinsky *et al.*, 1990), gavage (Ghanayem *et al.*, 1987b), or inhalation (Jönsson and Steen, 1978; Sabourin *et al.*, 1992b; Johanson, 1994). Route of administration, duration of exposure, dose, and differences in age have been shown to impact the urinary profile of 2-butoxyethanol metabolites and the overall elimination of absorbed 2-butoxyethanol.

Route Comparison

Ghanayem *et al.* (1987b) have shown that following gavage administration, in addition to 2-butoxyacetic acid in the urine, a glucuronide conjugate and sulfate conjugate are detected, although at much lower concentrations. The sulfate conjugate was observed only at low gavage doses (100 versus 500 mg/kg) and only in the first 8 hours of urine collection. Following inhalation exposure to 4.3, 49, or 438 ppm 2-butoxyethanol, there was an exposure-related increase in the proportion of butoxyethanol glucuronide to 2-butoxyacetic acid and a decrease in the percentage of 2-butoxyethanol exhaled in CO_2 (Sabourin *et al.*, 1992b). Ghanayem *et al.* (1987b) also showed that following a 500 mg/kg gavage dose

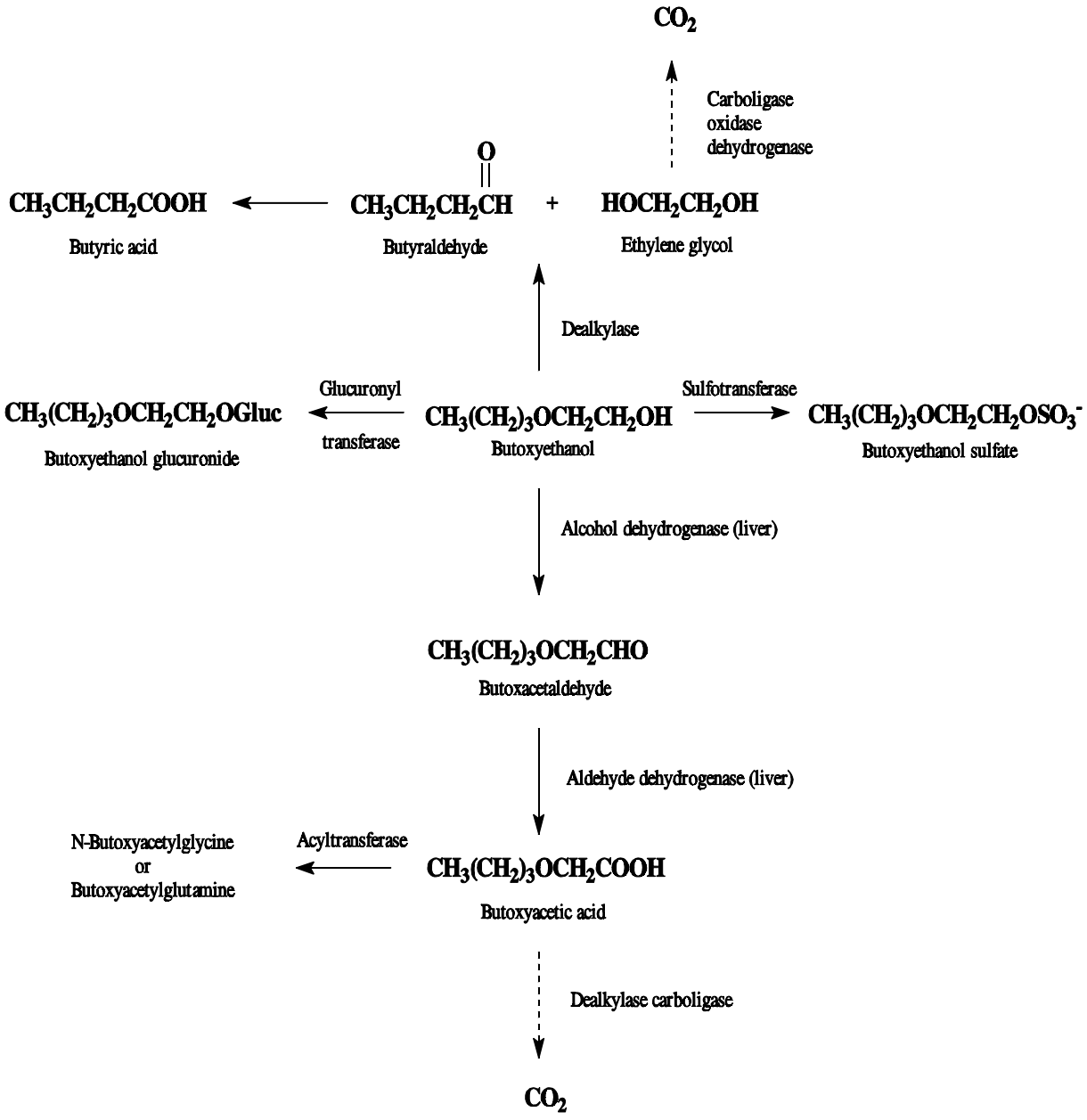

FIGURE 1
Scheme for Metabolism of 2-Butoxyethanol (ATSDR, 1998)

of 2-butoxyethanol, the major biliary metabolite was the 2-butoxyethanol glucuronide conjugate, followed by 2-butoxyacetic acid; this was the opposite of what was observed in urine. Ethylene glycol has been detected in the urine of rats following exposure to 2-butoxyethanol by inhalation (Sabourin *et al*., 1992b), by dermal application (Sabourin *et al*., 1992a), and in drinking water (Medinsky *et al*., 1990). Although ethylene glycol was not detected by Ghanayem *et al*. (1987b), this may merely reflect the difference in the position of the ^{14}C radiolabel on the 2-butoxyethanol molecule; these authors' label was on the butoxy moiety, whereas the ethanol moiety was used by the other authors.

Bartnik *et al*. (1987) injected male Wistar rats subcutaneously with [^{14}C]-2-butoxyethanol (118 mg/kg) and measured the elimination of radioactivity for 72 hours. The primary route of elimination was via urine, with 78% of the administered dose appearing in the urine by 72 hours. Less than 1% was found in feces, while 10% was exhaled as $^{14}CO_2$. In addition, Bartnik *et al*. administered 200 mg/kg of [^{14}C]-2-butoxyethanol topically to male and female Wistar rats and observed them for 48 hours. The highest amount of radioactivity in blood and plasma occurred 2 hours after application, with specific activity higher in plasma than blood. Measurements of 2-butoxyacetic acid in plasma followed the same qualitative course as 2-butoxyethanol. The authors concluded that the majority of 2-butoxyethanol absorbed was metabolized to 2-butoxyacetic acid. Approximately 29% and 25% of the administered dose was absorbed by males and females, respectively, with urine radioactivity accounting for 23% and 20% of the applied dose; there were no significant differences between genders. Over 95% of the radioactivity excreted in the urine was eliminated in the first 24 hours. For *in vitro* skin penetration studies, Bartnik *et al*. (1987) demonstrated that skin penetration rates were two to three times greater in hairless rat skin than in pig or human skin, with no significant difference in penetration rates between pig and human skin. Dugard *et al*. (1984) showed in *in vitro* studies that the rates of absorption for three glycol ethers by human abdominal whole skin differed. 2-Methoxyethanol was the most readily absorbed (2.82 mg/cm^2 per hour), followed by 2-ethoxyethanol (0.796 mg/cm^2 per hour), with 2-butoxyethanol (0.198 mg/cm^2 per hour) being the least absorbed. These studies indicate that for human skin *in vitro*, where evaporation is eliminated, absorption decreases with increased chain length of the glycol ethers.

Sabourin *et al*. (1992a) investigated the dermal absorption and elimination of 2-butoxy-[^{14}C]ethanol as well as that of methoxyethanol and ethoxyethanol in male F344 rats for 72 hours following dosing. Each glycol ether was applied (unoccluded) at three different doses: for 2-butoxyethanol, 122, 367, or 650 μmol per rat; for ethoxyethanol, 121, 387, or 881 μmol per rat; and for methoxyethanol, 114, 342, or 1,027 μmol per rat. Within these dose ranges for all three glycol ethers, the absorption and metabolism of each were found to be linearly related to the dose applied dermally. Regardless of chain length or dose administered, there was no major difference in absorption (20% to 27%) of the ethers. The percentage of 2-butoxyethanol absorbed (20% to 25%) is similar to that for Wistar rats reported by Bartnik *et al*. (1987). The majority of the absorbed dose for all three glycol ethers was detected in urine; for 2-butoxyethanol, this was 82% to 83%, for ethoxyethanol, 64% to 77%, and for methoxyethanol, 67% to 72%. The major urinary metabolite was the alkoxyacetic acid for each glycol ether. However, there were appreciable differences in the amount of alkoxyacetic acid for each. For 2-butoxyethanol, 2-butoxyacetic acid represented 65% to 71% of the total urinary metabolites, while the ethoxyacetic acid represented 50% to 58% and the methoxyacetic acid represented 23% to 46%. Only urine from 2-butoxyethanol-treated rats contained a glucuronide metabolite which accounted for 13% to 15% of the radioactivity in urine. Ethylene glycol was also detected in urine for all three ethers and represented 4% to 6% for 2-butoxyethanol, 13% to 18% for ethoxyethanol, and 9% to 11% for methoxyethanol. The amount of $^{14}CO_2$ eliminated in expired air was 4% to 6% for 2-butoxyethanol, 4% to 8% for ethoxyethanol, and 6% to 11% for methoxyethanol. Although the relative amount of glycol ether absorbed was similar for all three glycol ethers, there were differences in metabolism and elimination of the three.

Medinsky *et al*. (1990) also showed that, in drinking water studies, the fraction of the dose metabolized to ethylene glycol and CO_2 was inversely proportional to chain length of the glycol ethers, 2-methoxy-, 2-ethoxy-, and 2-butoxyethanol. The proportion of

2-butoxyacetic acid and, to some extent, CO_2 actually decreased with increasing drinking water concentrations of 290, 860, or 2,590 ppm 2-butoxyethanol, while ethylene glycol slightly increased For single-exposure inhalation studies, 2-butoxyacetic acid excretion has been shown to be linearly related to exposure concentration for up to 438 ppm 2-butoxyethanol, whereas ethylene glycol in urine decreases with increasing exposure concentration (Sabourin *et al.*, 1992b). In general, the amount of urinary glucuronide appears to increase with dose regardless of route.

Age Comparison

In single-dose gavage studies of 500 mg/kg 2-(1-[^{14}C]-butoxy)ethanol, Ghanayem *et al.* (1987c) showed that 4- to 5-week-old male F344 rats exhaled a significantly higher percentage of CO_2 than 9- to 13-week-old rats. Young rats also excreted a significantly higher percentage of the administered dose in urine, which contained more 2-butoxyacetic acid and less glucuronide conjugates than did urine from older rats. In another study, to further determine a dose and age effect, the authors also compared the effect of intravenous administration of [^{14}C]-2-butoxyethanol (31.25, 62.5, or 125 mg/kg) on 2-butoxyethanol toxicokinetics in 3- to 4-month-old and 12- to 13-month-old male F344 rats (Ghanayem *et al.*, 1990). They found both dose- and age-related effects on 2-butoxyethanol and 2-butoxyacetic acid kinetics. In younger rats administered 2-butoxyethanol intravenously, the area under the curve (AUC), maximum plasma concentration (C_{max}), and systemic clearance (Cl_S) of 2-butoxyethanol were dose dependent in that the AUC and C_{max} increased with increasing dose while Cl_S decreased with increasing dose. At the same doses, C_{max} and AUC of 2-butoxyethanol increased as a function of age. For 2-butoxyacetic acid, half-life ($t_{½}$), AUC, and C_{max} were increased relative to the dose of 2-butoxyethanol given and to the age of the rats. For 3- to 4-month-old rats, the $t_{1/2}$ in blood was approximately 10 minutes for 2-butoxyethanol and 3 hours for 2-butoxyacetic acid.

Repeated Exposure

The studies discussed previously primarily involved a single administration of radiolabeled 2-butoxyethanol in male rats. Johanson (1994) investigated the toxicokinetics of 2-butoxyethanol and 2-butoxyacetic acid in 4-month-old male rats following continuous inhalation exposure for 12 days to 20 or 100 ppm 2-butoxyethanol. Daily analyses indicated that the kinetics of 2-butoxyethanol and 2-butoxyacetic acid were linear up to 100 ppm. 2-Butoxyethanol and 2-butoxyacetic acid concentrations increased rapidly in tissue during the first 1 to 3 days and then more slowly during the rest of the study. At these concentrations there was no effect of exposure concentration on total blood clearance of 2-butoxyethanol (approximately 2.3 L/kg per hour) or the fraction of inhaled 2-butoxyethanol excreted in urine as 2-butoxyacetic acid (approximately 65%).

In conjunction with the long-term toxicology and carcinogenesis studies presented in this Technical Report, the National Toxicology Program performed toxicokinetic evaluations of 2-butoxyethanol and 2-butoxyacetic acid in the blood of male and female F344/N rats and B6C3F$_1$ mice following 1 day, 2 weeks, and 3, 6, 12, and 18 months of exposure to 2-butoxyethanol. 2-Butoxyacetic acid concentrations were determined in urine collected during the 16 hours after exposure at each of these time points except day 1. In addition, a separate set of male and female mice were maintained in the control chamber until they were approximately 19 months old, at which time they were exposed to 125 ppm 2-butoxyethanol for 3 weeks. The toxicokinetic parameters for 2-butoxyethanol and 2-butoxyacetic acid in blood, as well as the urine 2-butoxyacetic acid concentrations and the 19-month-old mouse study, are published by Dill *et al.* (1998). For male and female rats and mice, systemically absorbed 2-butoxyethanol was rapidly cleared from blood, independent of exposure concentration, throughout the study ($t_{½}$ for rat, less than 10 minutes; $t_{½}$ for mice, less than 5 minutes after 1 day of exposure). Increases in AUCs were proportional to increases in 2-butoxyethanol exposure concentrations, indicating linear 2-butoxyethanol kinetics. In contrast, the rate of 2-butoxyacetic acid elimination from blood decreased as the exposure concentration increased. Nonproportional increases in the 2-butoxyacetic acid AUC also indicated that 2-butoxyacetic acid was eliminated following dose-dependent, nonlinear kinetics. Overall, mice eliminated both 2-butoxyethanol and 2-butoxyacetic acid from blood faster than rats. Gender-related differences in 2-butoxyacetic acid elimination were most significant in rats, in that females were less efficient in clearing 2-butoxyacetic acid from the blood. Differences in renal excretion of 2-butoxyacetic acid

are possibly responsible for the gender-related difference in the 2-butoxyacetic acid blood profiles in rats. With repeated exposure, the rates of elimination for both 2-butoxyethanol and 2-butoxyacetic acid decreased in both species, resulting in longer residence times of 2-butoxyethanol and 2-butoxyacetic acid in the blood. 2-Butoxyethanol was rapidly cleared from the systemic circulation of 19-month-old naive mice exposed to 125 ppm, indicating clearance profiles similar to those of young mice. However, old mice eliminated 2-butoxyacetic acid from blood about 10 times more slowly than young mice after 1 day of exposure. This delayed elimination of 2-butoxyacetic acid in old mice was less obvious after 3 weeks of exposure compared to young mice exposed for 2 weeks, suggesting that there may be factors other than age that influenced the apparent difference in 2-butoxyacetic acid kinetics. Dill *et al.* (1998) concluded that the elimination kinetics of 2-butoxyethanol and 2-butoxyacetic acid following repeated 2-butoxyethanol exposure appeared to be dependent on species, gender, age, number of exposures, and exposure concentration.

In vitro Metabolism

The metabolism of 2-butoxyethanol, 2-ethoxyethanol, and 2-methoxyethanol in F344 rat and human hepatocytes *in vitro* was reported by Green *et al.* (1996). Each glycol ether, ^{14}C-labeled on the ethanol carbons, was incubated with rat or human hepatocytes for 4 hours at concentrations ranging from 0.02 to 10 mM. The major metabolite in each species for all the glycol ethers was the respective alkoxyacetic acid, followed by ethylene glycol. For 2-butoxyethanol an additional metabolite, a glucuronide conjugate, was found with each species. The percentage of glycol ether converted to the alkoxyacetic acid increased with glycol ether concentrations up to 10 mM in rat hepatocytes. However, in human hepatocytes, the percentage actually decreased between 0.02 and 0.2 mM. The following relative rate of alkoxyacetic acid formation from the glycols was determined: the 2-butoxyethanol rate was greater than that of 2-ethoxyethanol, followed by 2-methoxyethanol. This contrasted with ethylene glycol formation: 2-methoxyethanol had a greater rate than 2-ethoxyethanol, followed by 2-butoxyethanol. These findings are similar to those observed *in vivo*. Rat hepatocytes metabolized the glycol ethers at greater rates than human hepatocytes. For 2-butoxyethanol, at 0.2 mM, less than 1% of the 2-butoxyethanol remained after 4 hours in rat hepatocytes as opposed to about 55% in human hepatocytes. For 2-methoxyethanol, at 0.2 mM, 36% remained unmetabolized after 4 hours compared to 80% in human hepatocytes. The maximum velocity (V_{max}) for each glycol ether and the Michaelis constant (K_m) for all but 2-butoxyethanol were considerably higher for alkoxyacetic acid production in rat than in human hepatocytes. The V_{max} was 741 nmol/hour for 10^6 rat hepatocytes and 113 nmol/hour for 10^6 human hepatocytes for 2-butoxyethanol; for 2-ethoxyethanol, 1,519 nmol/hour (rat) and 71 nmol/hour (human); and for 2-methoxyethanol, 1,511 nmol/hour (rat) and 61 nmol/hour (human). The K_m was 6.6 mM (rat) and 1.2 mM (human) for 2-ethoxyethanol and 6.3 mM (rat) and 1.7 mM (human) for 2-methoxyethanol. For 2-butoxyethanol, the K_m for rat and human hepatocytes was the same, 0.9 mM.

Physiologic Based Pharmacokinetic Models

A number of physiologic based pharmacokinetic (PBPK) models have been developed based on short-term 2-butoxyethanol exposures by various routes for male rats and humans. Most of the models (Johanson, 1986; Johanson and Näslund, 1988; Shyr *et al.*, 1993; Corley *et al.*, 1994) have been thoroughly reviewed and models compared (ATSDR, 1998). In general, for these 2-butoxyethanol PBPK models, successive authors used data and results from previous authors and added new information to develop their models. Johanson (1986) and Johanson and Näslund (1988) developed a model for human exposure to 2-butoxyethanol by inhalation. This model utilized human and perfused rat liver data. Shyr *et al.* (1993) based their PBPK model on toxicokinetic data from male F344 rats exposed to 2-butoxyethanol by dermal application, by inhalation, and in drinking water. This model also included a metabolic pathway for 2-butoxyethanol. Corley *et al.* (1994) expanded the models of Johanson (1986) by modeling the disposition of 2-butoxyethanol and 2-butoxyacetic acid in humans and male F344 rats. This model included inhalation (whole body or nose/mouth only), oral (gavage or drinking water), intravenous infusion, and dermal (vapor or liquid) routes of administration; physiologic descriptions for rats; competing pathways for metabolism of 2-butoxyethanol; and measured partition coefficients determined by the authors for 2-butoxyethanol and 2-butoxyacetic acid in several rat tissues and human blood. Corley *et al.* (1997) modified this model further to include dermal

absorption of 2-butoxyethanol vapors for humans excluding secondary pathways for 2-butoxyethanol metabolism (conjugation and dealkylation) and including conditions for rest versus exercise. Toxicokinetic data from female rats or from male or female mice were not available to test against previous models. Lee *et al*. (1998), as part of the evaluation of the present 2-year inhalation studies with 2-butoxyethanol in male and female rats and mice, reported a PBPK model for 2-butoxyethanol and 2-butoxyacetic acid based on continuous exposure to 2-butoxyethanol for 18 months. The model incorporated data and results from previous models and accommodated exposure to 2-butoxyethanol by inhalation (whole body or nose only), dermal, gavage, or intravenous administration. In addition, because of the time course of repeated exposure and the associated need for time-dependent effects on physiologic and biochemic parameters, a number of additional parameters, functions, and mass balance differential equations were incorporated. Tissue compartments were revised relative to previous models in that a muscle compartment was included into the poorly perfused compartment, a kidney compartment was added for 2-butoxyethanol, and spleen was added as a separate compartment.

Humans

Controlled Experiments

In addition to 2-butoxyethanol occupational exposure assessments, there have been several controlled experiments whereby human volunteers have been exposed to 2-butoxyethanol percutaneously or by inhalation, and toxicokinetic assessments have been performed. Johanson *et al*. (1986b) exposed seven male volunteers to 20 ppm 2-butoxyethanol for 2 hours during light exercise on a bicycle ergometer. Respiratory uptake, derived from measurements of expired air over time, was determined to be 10.1 μmol/minute (1.2 mg/minute) or approximately 57% of the amount of inspired 2-butoxyethanol. Within 1 to 2 hours, 2-butoxyethanol blood concentrations reached a plateau of 7.4 μmol/L. The elimination half-time was 40 minutes; mean residence time, 42 minutes; total blood clearance time, 1.2 L/minute; and steady state volume of distribution, 54 L. Less than 0.03% of the total 2-butoxyethanol uptake was excreted in urine, whereas 2-butoxyacetic acid excretion represented 17% to 55% of the total 2-butoxyethanol uptake. In another experiment, Johanson and Johnsson (1991) exposed five male volunteers to 20 ppm 2-butoxyethanol for 2 hours during light exercise. Blood collected from a brachial vein at 2, 4, or 6 hours after exposure was analyzed for 2-butoxyacetic acid; concentrations ranged from approximately 22 to 60 μM with an average of approximately 45 μM reached within 2 to 4 hours. The half-life of 2-butoxyacetic acid in blood was estimated to be about 4 hours with a renal clearance of 23 to 39 mL per minute and an apparent volume of distribution of about 15 L, which the authors concluded represented considerable binding to blood proteins.

Johanson *et al*. (1988) determined the percutaneous absorption of 2-butoxyethanol in five male volunteers by immersing two to four fingers of one hand in neat 2-butoxyethanol for 2 hours. Blood was collected from the opposite hand (finger prick) during and up to 4 hours after exposure. Urine was collected for 24 hours and analyzed for 2-butoxyacetic acid. The skin of exposed fingers appeared to be more rigid, less elastic, and wrinkled. Within a few hours of exposure, a dry reticulate pattern with small fissures, some of which became erythematous, was observed but disappeared within 1 to 2 days. 2-Butoxyethanol was detected in the blood of all volunteers; however, the shape of the blood concentration profiles varied considerably between volunteers and experiments. Therefore, the percutaneous uptake of 7 to 96 nmol/cm^2 per minute (geometric mean was 20 nmol/cm^2 per minute) and the half-time of 2-butoxyethanol decay of 0.6 to 4.8 hours was highly variable. 2-Butoxyacetic acid was detected in the urine of each volunteer with a peak concentration occurring 3 hours after exposure and an average half-time of 3.1 hours. The amount of 2-butoxyacetic acid excreted was also highly variable (87 to 313 μmol). 2-Butoxyacetic acid excretion represented, on the average, 17% (2.5% to 39%) of the absorbed dose of 2-butoxyethanol.

To assess the percutaneous absorption component of inhalation exposure, four male volunteers breathed 50 ppm 2-butoxyethanol through a respiratory valve for 2 hours (Johanson and Boman, 1991). After a 1-hour nonexposure period, the volunteers' entire bodies were exposed for 2 hours to 50 ppm 2-butoxyethanol, followed by a 2-hour recovery period. The volunteers wore respirators to prevent inhalation exposure during the second 2 hours. In addition, each volunteer was also separately

challenged throughout each study to two different chamber environments, i.e., 23° C and 29% relative humidity or 33° C and 71% relative humidity. Blood was collected periodically over the 7-hour period from a finger prick. Blood 2-butoxyethanol concentrations appeared to reach a steady state during the second hour of the mouth-only exposure at approximately 3 μM, with an apparent blood clearance of 3.8 L per minute and a respiratory uptake of 11 μmol/minute. However, during percutaneous exposure, the concentration of 2-butoxyethanol increased to approximately 9 μM during the second hour of exposure, about three times higher than 2-butoxyethanol blood concentration during the inhalation exposure period. Percutaneous absorption was 31 μmol/minute, also about three times greater than the respiratory uptake. 2-Butoxyethanol half-life in blood following skin exposure averaged 34 minutes. In general, increased temperature and humidity increased blood 2-butoxyethanol concentrations during inhalation and dermal exposure; however, these differences were not statistically significant. The authors suggested that dermal uptake of 2-butoxyethanol accounts for approximately 75% of the total uptake during whole-body exposure.

Corley *et al*. (1997) investigated the impact of blood sampling location on measurement of dermal absorption of 2-butoxyethanol vapors in humans. These studies were initiated to provide an explanation for the apparently enhanced dermal absorption in humans following dermal exposure to 2-butoxyethanol vapors observed by Johanson and Boman (1991) and those authors' assertion that dermal absorption was a major contributor to total 2-butoxyethanol absorption in inhalation studies. Corley *et al*. compared blood collection by finger prick from the arm exposed to 2-butoxyethanol (Johanson method) to collecting blood by venous catheter in the unexposed arm. Six human volunteers were exposed, arm only, to 50 ppm 2-butoxyethanol for 2 hours and monitored for 24 hours during which blood and urine were collected. Neither 2-butoxyethanol nor 2-butoxyacetic acid was detected in blood from the catheterized arm for the first 30 minutes of exposure. 2-Butoxyethanol was rapidly cleared from the blood with $t_{½}$ of 0.66 hour. 2-Butoxyacetic acid concentrations exceeded those of 2-butoxyethanol at all time points, and 2-butoxyacetic acid was cleared less rapidly from the blood ($t_{½}$ = 3.3 hours). Peak blood concentrations were 0.037 μM for 2-butoxyethanol and 0.31 μM for 2-butoxyacetic acid. Using the finger prick method of collection, the 2 hour, 2-butoxyethanol blood concentration was 35.5 μM, about 1,500 times that obtained from the unexposed catheterized arm. 2-Butoxyethanol concentration in blood obtained from the finger prick was also about 37 times higher than the 2-butoxyacetic acid concentration (0.97 μM). This was the opposite of what was observed for the catheterized arm, where the blood 2-butoxyethanol concentration was roughly one tenth that of 2-butoxyacetic acid. The 2-butoxyacetic acid concentrations were more consistent when the two collection methods were compared, i.e., within a factor of four of each other. In blood from the catheterized arm, elimination half-times for 2-butoxyethanol (0.66 hours) and 2-butoxyacetic acid (3.3 hours) were consistent with the elimination half-times of 0.66 hours for 2-butoxyethanol and 4 hours for 2-butoxyacetic acid obtained following inhalation exposure under exercise conditions (Johanson *et al*., 1986b; Johanson and Johnsson, 1991). The authors concluded that blood collected by finger prick most likely represented both systemic concentration and local concentration of 2-butoxyethanol in venous blood draining the skin and was not an accurate representation of systemic 2-butoxyethanol absorption.

Occupational Exposure

A number of studies, which are detailed below, have provided biologic monitoring data following occupational exposure to 2-butoxyethanol. Occupations evaluated include those involved in varnish production, beverage packaging, automotive manufacturing and cleaning, office maintenance, and gravure printing. Preshift and postshift assessments were made. 2-Butoxyacetic acid concentration in urine was the primary end point for biologic monitoring. In some cases, only 2-butoxyacetic acid concentrations were reported. However, in others, free, conjugated, and total 2-butoxyacetic acid concentrations were stated.

Angerer *et al*. (1990) evaluated exposure to 2-butoxyethanol for 12 men working in a varnish production plant. Blood was collected at the end of each shift, whereas urine was collected prior to and following each shift. 2-Butoxyethanol workplace concentrations averaged 1.1 ppm (0.1 to 8.1 ppm). Blood 2-butoxyethanol concentrations averaged

121.3 μg/L (5 to 570 μg/L). Urine 2-butoxyacetic acid, taken at the same time blood was drawn, averaged 10.5 mg/L (0.6 to 30.3 mg/L). Urinary 2-butoxyacetic acid prior to starting a shift was considerably less, averaging 3.3 mg/L (0.1 to 14.3 mg/L). Söhnlein *et al*. (1993) determined the extent of 2-butoxyethanol exposure in 15 men and four women employed in the production of varnishes or their quality control. Preshift Monday and postshift Tuesday measurements were made. In the production area, the concentration of 2-butoxyethanol in air was determined to be 0.5 ppm (preshift) and 0.6 ppm (postshift). Prior to starting a shift, the average urinary concentration of 2-butoxyacetic acid was 0.2 mg/L, whereas the postshift concentration was 16.4 mg/L, indicating significant absorption of 2-butoxyethanol.

Haufroid *et al*. (1997) monitored urinary 2-butoxyacetic acid concentration in 31 male workers in a beverage packaging plant pre- and postshift. Twenty of the workers were transferring the decor to the cans, while the remainder were exposed to 2-butoxyethanol while spraying varnish on the inside of the cans. Workplace exposure averaged 0.76 ppm 2-butoxyethanol (0.37 to 1.29 ppm) for the decor transfer workers and 0.46 ppm (0.15 to 0.7 ppm) for the varnish sprayers. As in the studies reported previously, preshift urine 2-butoxyacetic acid concentrations were considerably lower than postexposure concentrations. For the decor transfer workers, preshift 2-butoxyacetic acid averaged 0.7 mg/L (0 to 2.8 mg/L) as opposed to a postshift 2-butoxyacetic acid average of 19.5 mg/L (0.9 to 78.9 mg/L). Likewise, the varnish sprayers had comparable average 2-butoxyacetic acid concentrations of 1.0 mg/L (0 to 5.2 mg/L) for preshift and 14.2 mg/L (0.9 to 35.5 mg/L) for postshift measurements. These measurements for 2-butoxyacetic acid are in close agreement with those reported by Angerer *et al*. (1990) and Söhnlein *et al*. (1993).

Vincent *et al*. (1993) reported the occupational exposure to 2-butoxyethanol in municipal government workers who cleaned windows in automobiles and workers cleaning office windows. 2-Butoxyethanol concentrations in window cleaning products ranged from 0.9% to 21.2%. 2-Butoxyethanol concentrations monitored in the workplace air ranged from less than 0.1 to 7.33 ppm for automobile cleaners and less than 0.3 to 0.73 ppm for office cleaners. Preshift urinary concentrations ranged from less than 2 to 98.6 mg 2-butoxyacetic acid/g creatinine for automobile washers versus less than 2 to 4.6 mg 2-butoxyacetic acid/g creatinine for office cleaners. End-shift concentrations were considerably higher, ranging from 12.7 to 371 mg 2-butoxyacetic acid/g creatinine and 2 to 3 mg 2-butoxyacetic acid/g creatinine for the two occupations, respectively. Pre- and postshift 2-butoxyacetic acid concentrations for office workers were similar, indicating a low level of exposure during work hours and possible exposure to 2-butoxyethanol in products outside the workplace.

Rettenmeier *et al*. (1993) monitored the urine of six lacquerers at an automotive manufacturing plant to determine 2-butoxyethanol exposure. Although exposure conditions were stated as being similar, no workplace environmental monitoring was reported. Each worker used a 2-butoxyethanol-containing detergent to clean automotive body parts. Urine samples were collected from each worker at the end of a Friday shift and on Monday prior to beginning a new shift and analyzed for 2-butoxyacetic acid and 2-butoxyacetic acid glutamine conjugate. The Monday samples contained only traces of either metabolite (data not reported). Postshift samples taken on the previous Friday contained both metabolites in almost equimolar quantities; however, the concentrations of each were highly variable between individuals although consistent for each individual. Concentrations ranged from 0.13 to 5.91 mmol 2-butoxyacetic acid/L and 0.12 to 2.45 mmol glutamine conjugate/L. The authors concluded that measurement of urinary 2-butoxyacetic acid alone was not sufficient for biologic monitoring of 2-butoxyethanol exposure in humans.

In similar studies, Sakai *et al*. (1993) measured 2-butoxyacetic acid concentrations at the end of an8-hour workday in the urine of nine workers engaged in gravure printing. The workers were exposed during the workday to an average 2-butoxyethanol concentration of 0.64 ppm (0.4 to 0.8 ppm). Urine 2-butoxyacetic acid concentrations averaged 3.92 mg 2-butoxyacetic acid/g creatinine (1.3 to 9.9 mg/g C). In another study, Sakai *et al*. (1994) assessed exposure of five workers throughout a workweek in a semiconductor factory where they were engaged in polymerization of resin dissolved in 2-butoxyethanol. The workplace was monitored for

2-butoxyethanol. Individual 2-butoxyethanol concentrations were not reported; however, exposures were reported to be less than 0.8 ppm. Urine concentrations of free and conjugated 2-butoxyacetic acid were measured. As expected, free and conjugated 2-butoxyacetic acid concentrations increased at the end of each workday, with a small amount of conjugated 2-butoxyacetic acid detected prior to the start of the next workday. During the first 2 days of the workweek, more conjugated 2-butoxyacetic acid was excreted than toward the end of the week; however, conjugated 2-butoxyacetic acid always contributed the greatest portion of total 2-butoxyacetic acid excreted, 71% (44% to 92%). The authors concluded that the decline in excretion of conjugated 2-butoxyacetic acid indicated that the metabolic capacity for 2-butoxyacetic acid conjugation was gradually depressed.

TOXICITY

Experimental Animals

Extensive reviews of the toxicity of 2-butoxyethanol and other alkyl glycol ethers have been published (NIOSH, 1990; *Patty's*, 1994; ATSDR, 1998; CIRP, 1996; Ghanayem, 1996). In general, alkyl glycol ethers such as 2-methoxy-, 2-ethoxy-, and 2-butoxyethanol have been shown to induce reproductive and developmental effects or hematologic effects. As the length of the alkyl chain increases, hematologic effects predominate, whereas as the alkyl chain length decreases, reproductive and developmental effects are more common. The alkoxyacetic acids (2-methoxy-, 2-ethoxy-, and 2-butoxyacetic acid) are the primary metabolites of these alkyl glycol ethers and are considered to be the toxic agents. Inhibition of the metabolism of the glycol ether to its corresponding alkoxyacetic acid has been shown to reduce or abolish the resulting testicular atrophy, teratogenicity, and immunotoxicity of 2-methoxyethanol and the hemolytic effects of 2-butoxyethanol.

The LD_{50} values for 2-butoxyethanol vary widely depending on the route of administration, duration of exposure, and species involved. The oral LD_{50} for rats is about 1,500 mg/kg (530 to 3,000 mg/kg); for mice, 1,230 mg/kg; for rabbits, approximately 350 mg/kg; and for guinea pigs, 1,200 mg/kg. The dermal LD_{50} for rabbits ranges from 72 to 638 mg/kg and for the guinea pig from 205 to 4,800 mg/kg. The LC_{50} values are 486 ppm for male and 450 ppm for female F344 rats in 4-hour inhalation studies and 700 ppm in mice in 7-hour studies. The intravenous LD_{50} is 340 mg/kg for rats, 1,130 mg/kg for mice, and 280 mg/kg for rabbits (ITII, 1981; Tyler, 1984; *Patty's*, 1994; ATSDR, 1998; CIRP, 1996).

2-Butoxyethanol toxicity has been demonstrated in animals following inhalation, gavage, injection, or dermal exposure. In a series of experiments, Werner *et al*. (1943a,b,c), exposed dogs, mice, and rats to 2-butoxyethanol vapors. Dogs were exposed to 415 ppm 2-butoxyethanol 7 hours per day, 5 days per week for 12 weeks. A maximum decrease in erythrocyte count, hemoglobin concentration, and hematocrit value was observed after 4 to 6 weeks of exposure and continued until the end of the study. In other studies, white Swiss mice were exposed to concentrations of 390 to 1,210 ppm 2-butoxyethanol for 7 hours. Mortality occurred before the end of exposure for mice exposed to 770 ppm or greater and within 32 hours at concentrations above 390 ppm. Respiratory distress, hemoglobinuria, and splenic congestion were noted. Wistar rats were exposed to 320 ppm 2-butoxyethanol 7 hours per day, 5 days per week for 5 weeks; significant decreases in hemoglobin concentration and erythrocyte count were observed after 1 week.

Carpenter *et al*. (1956) exposed rats, mice, rabbits, dogs, monkeys, and guinea pigs to 100 to 400 ppm 2-butoxyethanol for up to 90 days. One rhesus monkey exposed for 30 days to 210 ppm 2-butoxyethanol exhibited increased erythrocyte fragility (4th exposure) and increased fibrinogen (14th exposure). At the end of the study, erythrocyte count and hemoglobin concentration were reduced to levels half that at the start of the study. A male and a female monkey exposed to 100 ppm 2-butoxyethanol for 90 days had increased erythrocyte fragility and decreased numbers of erythrocytes. The female was more severely affected. Erythrocyte fragility was observed in rats within 4 hours of exposure to 62 ppm 2-butoxyethanol, whereas hemolysis and hemoglobinuria were observed within 2 to 3 hours in female rats exposed to 432 ppm. Females were usually more severely affected. Erythrocyte fragility was also observed in mice (100 ppm) and rabbits (125 ppm) following 7-hour exposure. The extent of

increased erythrocyte fragility did not increase in mice when exposure to 100 ppm was continued for 90 days. Dogs exposed to 385 ppm 2-butoxyethanol for at least 8 days also showed increased fragility, whereas guinea pigs exposed for 30 days to 500 ppm 2-butoxyethanol did not show this effect. In addition, rats (107 ppm) and mice (200 ppm) had increased liver weights after 30 and 60 days exposure, respectively. Cloudy swelling of the liver and convoluted tubules of the kidney were observed in female rats.

Dodd *et al*. (1983), in two separate experiments, exposed male and female F344 rats 6 hours per day to 0, 20, 86, or 245 ppm 2-butoxyethanol for 9 days or 0, 5, 25, or 77 ppm 2-butoxyethanol, 5 days per week for 13 weeks. Rats exposed to 245 ppm exhibited significant decreases in erythrocyte count, hemoglobin concentration, and mean cell hemoglobin concentration and increases in nucleated erythrocyte, reticulocyte, and lymphocyte counts at 9 days. Liver weights were increased. Similar but less marked effects were observed in rats exposed to 20 ppm. Female rats exposed to 77 ppm for 6 weeks had statistically significant decreases in erythrocyte count and hemoglobin concentration accompanied by an increase in mean cell hemoglobin value; these effects were still present at the end of the 13-week study, although they were less severe. Male rats exposed to 77 ppm 2-butoxyethanol (after 66 exposures) had a 5% decreased erythrocyte count, although the decrease was not statistically significant. No exposure-related effects on urine or serum chemistries, body or organ weights, or microscopic lesions were observed.

Nelson *et al*. (1984), in a range-finding study prior to an inhalation teratology study, exposed three or four female Sprague-Dawley rats to 250 to 500 ppm 2-butoxyethanol for 6.5 to 7 hours. Deaths occurred within 18 to 36 hours at all exposure concentrations with the majority occurring at 450 ppm and higher. Various degrees of hematuria were noted. In addition, the survivors from each concentration were maintained individually, and approximately 1 week past exposure it was noted that the distal half of the tail became necrotic and sloughed off or was chewed off. This same tail effect was reported by Dow Chemical Corporation in 1981 (presented in ATSDR, 1998) in female F344 rats following a single gavage dose of 1,000 mg 2-butoxyethanol/kg body weight. Hardin *et al*. (1984), while conducting a dermal administration comparative teratology study in SPF Sprague-Dawley rats with several glycol ethers, observed overt toxicity in dams dosed with 2-butoxyethanol. The glycol ethers were administered in equimolar doses with 0.35 mL neat 2-butoxyethanol administered four times daily (every 2.5 hours) on gestation days 7 to 16. During the first day of treatment, burgundy-colored urine was noted, and by the end of the first day, the dams were showing signs of ataxia. With subsequent treatments, ataxia led to inactivity and ultimately death for 10 of the 11 dams (days 3 through 7 of dosing). As reported previously, the rats' tails blackened distally and were gradually eaten away as the apparent necrosis progressed.

Tyler (1984) gave mice gavage doses of 500, 1,000, or 2,000 mg/kg 2-butoxyethanol 5 days per week for 5 weeks. All mice receiving 2,000 mg/kg died. Mice treated with 500 mg/kg or higher had reduced erythrocyte counts. Grant *et al*. (1985) gavaged male F344 rats with 500 or 1,000 mg 2-butoxyethanol/kg body weight daily for 4 consecutive days and then observed them for 3 weeks. Spleen, liver, kidney, and thymus weights were increased for up to a week after dosing. Only liver and spleen weights remained elevated at day 22. Mean body weight gain was reduced only at 1,000 mg/kg. Hematologic effects observed on the fourth day of dosing included decreases in erythrocyte count, hemoglobin concentration, and hematocrit value and marked elevated mean cell volume, mean cell hemoglobin value, and reticulocyte count. These effects returned to normal during the recovery period, and by day 22, only an increase in mean cell volume was noted. Bone marrow hyperplasia and a marked increase in splenic extramedullary hematopoiesis were observed. Unlike 2-butoxyethanol, 2-methoxyethanol given to rats at 100 and 500 mg/kg during the same period had a minimal effect on erythrocytes. However, exposure to 2-methoxyethanol did result in significantly reduced leukocyte counts, as represented by reductions in neutrophils and lymphocytes that remained until day 22. Treatment with 2-methoxyethanol resulted in reduced spleen, kidney, testes, and thymus weights, with testes weight remaining significantly reduced at day 22. Bone marrow was hemorrhagic in the 500 mg/kg group at day 1 and appeared to be associated with sinus endothelial cell damage. Normal extramedullary hematopoiesis of the spleen

was abolished at the end of dosing and had returned to normal by day 22. Of importance was the severity of the testicular atrophy, which included disruption of the normal tubular architecture, degenerative changes in spermatocytes, and absence of spermatozoa in the epididymides. Thymic lymphocyte depletion was noted only at day 1.

In gavage studies of longer duration, Krasavage (1986) dosed male COBS CD (SD) BR rats with 0, 222, 443, or 885 mg/kg 2-butoxyethanol, 5 days per week for 6 weeks. There was a dose-dependent decrease in mean body weight gain. Although rats exposed to 2-butoxyethanol ate less than controls early in the study, only those treated at 885 mg/kg had significantly reduced feed consumption. Relative liver, kidney, and spleen weights were increased, primarily in the 885 mg/kg dose group. At the end of dosing, there were dose-related decreases in erythrocyte counts, hemoglobin concentrations, and mean cell hemoglobin concentrations with increases in mean cell volumes and mean cell hemoglobin values. Hepatocytomegaly was observed at 885 mg/kg. In addition, there was hemosiderin accumulation in the liver (885 mg/kg only) and proximal convoluted tubules of the kidney (all doses). Minimal to mild hyperkeratosis and acanthosis were observed in the stomach (forestomach or glandular stomach was not specified). Dosing did not affect the testes, thymus, bone marrow, or leukocytes. These results are consistent with those of Grant *et al*. (1985) using male F344 rats, except that those authors observed bone marrow hyperplasia.

In drinking water studies, male Sprague-Dawley rats were exposed to 0, 2,000, or 6,000 ppm 2-butoxyethanol or 2-methoxyethanol, and female Sprague-Dawley rats were exposed to 0, 1,600, or 4,800 ppm 2-butoxyethanol or 2-methoxyethanol for 21 days (Exon *et al*., 1991). Male and female rats exposed to the highest concentration of either chemical consumed significantly less water. Male rats exposed to high doses of either chemical and females exposed to both doses of 2-butoxyethanol gained significantly less weight than controls. The thymus was significantly smaller in male and female rats exposed to 2-methoxyethanol, while the testis weight in males was greatly reduced at the high dose. No significant organ weight effects were noted in rats drinking water containing 2-butoxyethanol. No 2-butoxyethanol-related lesions were observed in the thymus, liver, kidney, or testis, whereas atrophy was noted in the thymus of 2-methoxyethanol-treated rats.

The NTP (1993b) conducted 13-week drinking water studies in male and female F344/N rats and B6C3F$_1$ mice with 750 to 6,000 ppm 2-butoxyethanol. Estimates of compound consumption were 70 to 500 mg/kg for rats and 100 to 1,300 mg/kg for mice. All rats and mice survived to the end of the study. Exposure-related reductions in mean body weight gain were seen in rats and mice. There was no effect on the testis weight of rats or mice. Although thymic weights were reduced in rats, these reductions were significantly less severe than those observed following exposure to either 2-methoxyethanol or 2-ethoxyethanol. In addition, male and female rats had exposure-related increased relative liver and kidney weights. There were increased incidences of bone marrow hyperplasia; pigmentation and hematopoiesis of the spleen; and pigmentation, degeneration, and cytoplasmic alteration of the liver in rats. There were no treatment-related histopathologic findings in mice. Histopathologic effects in rats were consistent with effects on the hematopoietic system which resulted in a progressive anemia. The anemia caused by 2-butoxyethanol was characterized as macrocytic, hypochromic, and regenerative with increased bone marrow cellularity and marginal thrombocytopenia.

The ethylene glycol alkyl ethers have been shown to affect the hematopoietic system. For 2-butoxyethanol, this effect is the primary toxicologic event in animals. Over the last 50 years, a number of scientists have investigated these effects (Werner *et al*., 1943a,b,c; Carpenter *et al*., 1956; Dodd *et al*., 1983; Grant *et al*., 1985; Krasavage, 1986; Bartnik *et al*., 1987; Ghanayem, 1989; Ghanayem and Sullivan, 1993; Ghanayem *et al*., 1987a,b,c, 1989, 1990, 1992). A number of comprehensive reviews describe the 2-butoxyethanol-associated hematologic toxicity in animals compared to humans (*Patty's*, 1994; ATSDR, 1998; CIRP, 1996; Ghanayem, 1996); therefore, only a summary of the 2-butoxyethanol-induced hematotoxicity is provided here. 2-Butoxyethanol causes hemolysis of erythrocytes *in vivo* leading to an anemia and secondary effects on other organs (liver, kidney, spleen, and bone). Following exposure, 2-butoxyethanol caused increased osmotic fragility of erythrocytes (Carpenter *et al*., 1956) resulting in increased sensitivity to osmotic lysis. The hemolytic effects of 2-butoxyethanol are exerted by its major

metabolite, 2-butoxyacetic acid (Carpenter *et al.*, 1956; Bartnik *et al.*, 1987; Ghanayem *et al.*, 1987a). Inhibition of alcohol dehydrogenase by pyrazole or aldehyde dehydrogenase by cyanamide (Ghanayem *et al.*, 1987a) or administration of either ethanol, n-propanol, or n-butanol with 2-butoxyethanol (Morel *et al.*, 1996) inhibits the hemolytic effect of 2-butoxyethanol. There is an apparent species sensitivity to the 2-butoxyethanol-induced lysis; rats and mice are more sensitive, followed by rabbits and primates. Pigs, dogs, cats, guinea pigs, and humans are relatively insensitive (Ghanayem and Sullivan, 1993). Several studies have shown that females of several species, including monkeys (Carpenter *et al.*, 1956) and rats (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; NTP, 1993b), are more susceptible than males to the hematologic effects of 2-butoxyethanol administration. Whether females of other species are more sensitive than males is unknown because most of the toxicity and mechanism studies have been conducted only in males. In addition, it has been reported that young rats are less sensitive to hemolysis caused by 2-butoxyethanol exposure than older rats (Ghanayem *et al.*, 1987c). It has been shown that repeated exposure or pretreatment with high doses of 2-butoxyethanol may result in a tolerance due to selective loss of older erythrocytes followed by an increase in newly formed erythrocytes that appear to be less sensitive (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995).

In rats, lysis is preceded by erythrocyte swelling, decreased adenosine triphosphate levels (Ghanayem *et al.*, 1989), and reduced deformability (Udden and Patton, 1994). The erythrocytes have a tendency to agglutinate and release hemoglobin, which forms visible precipitates (Udden and Patton, 1994). Erythrocyte morphologic alterations of stomatocytosis, spherocytosis, fragmentation, and formation of ghost cells have been reported (Ward *et al.*, 1989; Udden and Patton, 1994). Human erythrocytes *in vitro* are less susceptible than rat erythrocytes to hemolysis and deformability by 2-butoxyacetic acid (Bartnik *et al.*, 1987; Ghanayem, 1989; Udden, 1994). In addition, when 2-butoxyacetic acid was incubated with erythrocytes obtained from individuals with hereditary spherocytosis or sickle cell disease, two human disorders marked by chronic hemolysis, there was no increase in hemolysis, no changes in mean cell volume or morphology, and no changes in deformability (Udden, 1994).

Secondary to the 2-butoxyethanol-induced hemolysis and depending on the dose of 2-butoxyethanol, there may be increased incidences of hematopoietic cell proliferation in the spleen, pigmentation/hemosiderin accumulation in the Kupffer cells of the liver and proximal convoluted tubules of the kidney, and hyperplasia and increased cellularity of the bone marrow with a reticulocytosis and increase in nucleated erythrocytes and hemoglobinuria (Werner *et al.*, 1943a,b,c; Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Grant *et al.*, 1985; Krasavage, 1986; Ghanayem, 1987c; NTP, 1993b). In addition, *in vitro* studies have shown that exposure to 2-butoxyethanol may have a direct toxic effect on hematopoiesis (Ruchaud *et al.*, 1992).

Humans

Workers have reported eye, skin, and respiratory tract irritations as well as headache, dizziness, lightheadedness, and nausea following exposure to 2-butoxyethanol (ATSDR, 1998). Several acute poisoning cases have been reported. Rambourg-Schepens *et al.* (1988) reported a suicide case in which a 50-year-old woman ingested 250 to 500 mL of window cleaner containing 12% 2-butoxyethanol. When admitted to the hospital, she was described as comatose with labored respiration. Metabolic acidosis, hypokalemia, rise in serum creatinine, hemoglobinuria, and oxaluria were observed. The hemoglobinuria was paralleled by reduced erythrocyte count, hematocrit value, and hemoglobin concentration. Urinary 2-butoxyacetic acid and oxalate were measured during 8 days in the hospital. 2-Butoxyethanol was excreted the greatest the first 24 hours after ingestion (approximately 2.5 g 2-butoxyethanol/g creatinine), whereas 2-butoxyacetic acid excretion peaked 2 days after ingestion at 40 g 2-butoxyacetic acid/g creatinine and was still measurable 1 week after ingestion. On arrival, urinary oxalate was high (40 g/g creatinine). The authors concluded that the high urinary concentrations of 2-butoxyethanol were a result of overload of the two main metabolic pathways for 2-butoxyethanol. They also concluded that 2-butoxyethanol was also hydrolyzed to ethylene glycol, which was further metabolized to oxalate. ATSDR (1998) estimated that the dose was between 467 and 933 mg/kg.

In another suicide attempt (Gijsenbergh *et al.*, 1989), a 23-year-old woman weighing 64 kg ingested 250 to 500 mL of a window cleaner containing 12.7%

2-butoxyethanol and 3.2% ethanol. The dose was estimated at 400 to 500 mg/kg 2-butoxyethanol. On arrival, the patient was comatose with obstructive respiration and was placed on a respirator. Blood evaluation was normal; however, within an hour, she was in metabolic acidosis, and hemodialysis was started. On the second day, her hemoglobin concentration decreased from 11.9 g/L to 8.9 g/L at the same time she was excreting hemoglobin in her urine. 2-Butoxyethanol and 2-butoxyacetic acid concentrations were measured in the dialysis fluid, and 2-butoxyacetic acid was measured in the urine. The half-life of 2-butoxyethanol was 210 minutes. 2-Butoxyacetic acid in urine reached a maximum (about 7.5 g/g creatinine) 24 hours after arrival. Unlike the first case, there was no oxaluria. The authors concluded that hemodialysis eliminating the 2-butoxyethanol in the blood prevented the oxaluric situation observed in the previous case.

Bauer *et al*. (1992) reported a case of a 53-year old male alcoholic who attempted suicide by drinking approximately 500 mL of a household cleaning fluid (9.1% 2-butoxyethanol, 2.5% ethanol). The patient was comatose and in metabolic acidosis and hypoxemia. Serum 2-butoxyethanol concentration was 5.28 g/L. 2-Butoxyethanol was not detected in gastric lavagate or urine. Hemoglobin (9.4 g/dL) and hematocrit (25%) were reduced. Respiratory support and hemodialysis were employed, and the patient recovered.

Several controlled inhalation studies with 2-butoxyethanol have been conducted in humans. Carpenter *et al*. (1956) exposed human volunteers to an atmosphere containing 98, 113, or 195 ppm 2-butoxyethanol for 4 or 8 hours. No evidence of erythrocyte fragility, hemolysis, or a systemic toxic effect was reported. The volunteers complained of nasal and eye irritation, and some reported nausea, headaches, a disagreeable metallic taste, and occasional belching. 2-Butoxyacetic acid concentrations in the urine of individuals exposed to 98 ppm ranged from 75 to 250 mg.

Johanson *et al*. (1986b) exposed seven male volunteers to an atmosphere containing 20 ppm 2-butoxyethanol for 2 hours during light exercise on a bicycle ergometer. None of the volunteers complained of or showed evidence of adverse effects that could be attributed to 2-butoxyethanol exposure. There was no effect of exposure on pulmonary ventilation, respiratory frequency, or heart rate. In another study, Johanson and Boman (1991) orally exposed four male volunteers to 50 ppm 2-butoxyethanol for 2 hours, followed by 1 hour with no exposure and then by 2 hours of dermal exposure to 50 ppm 2-butoxyethanol to determine percutaneous absorption of 2-butoxyethanol vapors. No treatment-related toxicity was observed. Johanson *et al*. (1988) reported the percutaneous exposure of five men to neat 2-butoxyethanol. The volunteers placed four fingers in a jar of 2-butoxyethanol for 2 hours. The skin of the exposed fingers appeared to be more rigid, less elastic, and wrinkled after exposure. Within a few hours of exposure, a dry reticulate pattern with several fissures, some of which became erythematous, was observed but disappeared within 1 to 2 days. No other treatment-related effect was observed.

Greenspan *et al*. (1995) exposed 201 adults to 0.2 mL 2-butoxyethanol (10% aqueous solution, the highest concentration used in cosmetic products) on the back. The dosed area was occluded. Testing included dosing, removal of the patch within 24 hours, evaluating the exposed area at 48 hours, and application of an identical patch to the same location. The subjects received nine such applications over a 6-week period. By the end of the 6 weeks, 25% of the subjects showed slight or definite erythema. Followingapplication to a naive area at 6 weeks, slight erythema was observed in seven subjects at 48 hours and 12 at 72 hours; one subject had definite erythema at 72 hours. No other effects were noted.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

The short-chain alkyl glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, and their alkoxyacetic acid metabolites are potent male reproductive toxicants and teratogens in several species (Hardin, 1983; Hardin *et al*., 1984, 1987; Nagano *et al*., 1984; Wier *et al*., 1987; Morrissey *et al*., 1989; Heindel *et al*., 1990; Schwetz and Harris, 1993). However, neither 2-butoxyethanol nor 2-butoxyacetic acid has clearly been shown to cause reproductive effects.

There was no effect of 2-butoxyethanol exposure on the male rat or mouse reproductive system in several

repeated exposure studies via inhalation, gavage, or drinking water (Dodd *et al.*, 1983; Nagano *et al.*, 1984; Grant *et al.*, 1985; Krasavage, 1986; Exon *et al.*, 1991; NTP, 1993b).

Foster *et al.* (1987) compared the *in vivo* and *in vitro* testicular effects produced by the alkoxyacetic acid metabolites of 2-butoxy-, 2-ethoxy-, and 2-methoxyethanol. Wistar rats were gavaged once with 0, 174, 434, or 868 mg/kg 2-butoxyacetic acid; 137, 342, or 684 mg/kg 2-ethoxyacetic acid; and 118, 296, or 592 mg/kg 2-methoxyacetic acid and followed for 14 days. All doses of all three acids caused decreased mean body weight gain during the first 2 days with recovery by day 14. Animals dosed with 868 mg/kg 2-butoxyacetic acid showed evidence of hematuria throughout the study. Only 2-methoxyacetic acid (592 mg/kg) caused a significant decrease in testis weight. Histologic evidence of testicular damage was observed in all 2-methoxyacetic acid groups; similar effects in 2-ethoxyacetic acid groups were less severe than those in 2-methoxyacetic acid groups. No evidence of testicular damage was observed in 2-butoxyacetic acid treated groups. Likewise, in an *in vitro* study with mixed cultures of Sertoli and germ cells, 2-methoxyacetic acid and, to a lesser extent, 2-ethoxyacetic acid enhanced germ cell loss. 2-Butoxyacetic acid at equimolar concentrations had no effect on the cultured cells. All acids were tested at 0 to 10 mM. For the testis, glycol ether-induced toxicity was more apparent in the shorter alkyl chain alkoxyacetic acids; 2-methoxyacetic acid was more sensitive than 2-ethoxyacetic acid, followed by 2-butoxyacetic acid.

Heindel *et al.* (1990) reported the effect of 2-butoxyethanol treatment in drinking water (0%, 0.5%, 1.0%, or 2.0%) to male and female Swiss (CD-1®) mice in a 98-day continuous breeding study. In a 2-week pilot study, males and females treated with 2.5% or greater 2-butoxyethanol lost weight, and mortality occurred at 5.0%. In the continuous breeding study, 13 of 20 females in the 2.0% group died compared to 6 in the 1.0% group. Male mice given 1.0% or 2.0% 2-butoxyethanol lost weight during the study, and females in the 2.0% group gained considerably less than controls. Treated mice consumed less water than controls. At doses causing maternal toxicity, there was a reduction in the number of live pups per litter, proportion of pups born alive, and live pup weight. Following the continuous breeding study, a crossover mating study using F_0 mice from control and 1.0% 2-butoxyethanol groups was performed. In female mice treated with 1.0% 2-butoxyethanol and mated with control males, there was a significant reduction in the fertility index (number fertile/number with copulatory plugs) and a reduction in the number of live pups per litter. There was no effect in mating index (number with copulatory plugs/number cohabited). Other than reduced body weight, there were no treatment-related effects on sperm indices or histopathology in male mice treated with 1.0% 2-butoxyethanol. In addition to body weight reduction, female mice treated with 1.0% 2-butoxyethanol had increased liver weights. There were no histopathologic effects or effects on estrous cycle stages or average cycle length. However, 7 of 13 females had cycles longer than 7 days compared to controls in which 9 of 38 were abnormal. Because of the lack of sufficient pups from the first generation study at 1.0%, the second generation study was conducted using the 0.5% group. There were no treatment-related effects on mating or fertility indices or other reproductive parameters. The only effects related to 2-butoxyethanol exposure were increased liver weights in males and females and increased kidney weights in females.

A number of developmental toxicity studies, both *in vivo* and *in vitro*, have been conducted with 2-butoxyethanol. Hardin *et al.* (1987) reported the effects of 2-butoxyethanol gavage treatment (1,180 mg/kg per day) in Swiss (CD-1®) mice during gestation days 6 and 13. The dose selected was the LD_{10} determined by a previous pilot study. During the study, 10 of the 50 dams died and the survivors had a significant reduction in weight gain when compared to controls. The number of viable litters was significantly reduced from controls. There were no treatment-related effects on neonatal response variables. Schwetz and Harris (1993) reported the results of two developmental toxicity studies in rats treated with 2-butoxyethanol. Rats were gavaged with 30 to 200 mg/kg 2-butoxyethanol during gestation days 9 to 11 or 30 to 300 mg/kg during days 11 to 13. Maternal toxicity, but not developmental toxicity, was observed in both studies at all doses.

Wier *et al.* (1987) investigated the potential teratogenic and postnatal growth effects in Swiss (CD-1®) mice given 0, 350, 650, 1,000, 1,500, or

2,000 mg 2-butoxyethanol/kg by gavage during gestation days 8 to 14. Mortality occurred in all six dams in the 2,000 mg/kg group and three of six in the 1,500 mg/kg group. There were significant increases in resorptions in the surviving 1,000 and 1,500 mg/kg females. There was no evidence of 2-butoxyethanol-related toxicity during the postnatal assessment.

Nelson *et al*. (1984) exposed pregnant Sprague-Dawley rats to 150 or 200 ppm 2-butoxyethanol by inhalation 7 hours per day during gestation days 7 to 15. Hematuria was noted in the dams only on day 1 of exposure. There were no other treatment-related effects in the dams, and there were no teratogenic effects due to exposure to 2-butoxyethanol.

In a teratology study reported by Tyl *et al*. (1984), pregnant F344 rats and New Zealand white rabbits were exposed to 0, 25, 50, 100, or 200 ppm 2-butoxyethanol on gestation days 6 to 15 (rats) or 6 to 18 (rabbits). Significant reductions in rate of weight gain and water consumption were observed in dams exposed to 200 ppm. Feed consumption was decreased in dams exposed to 100 or 200 ppm 2-butoxyethanol. Also of interest is that during the exposure period, dams exposed to 200 ppm had tails that were deemed discolored and ulcerated. These tails were missing later, as previously reported. Following sacrifice on gestational day 21, gravid uterine weight was significantly reduced and absolute and relative spleen weights and relative kidney weight were elevated in the 200 ppm group when compared to controls. In addition, dams exposed to 100 or 200 ppm 2-butoxyethanol had reduced erythrocyte counts and increased mean cell hemoglobin concentration. Hematocrit value was significantly increased only in dams exposed to 200 ppm. The authors concluded that these findings are consistent with destruction of mature erythrocytes and release of immature and/or young erythrocytes into the peripheral circulation. For rabbit dams there was treatment-related mortality, depressed body weight during the exposure period, and increases in spontaneous abortions. There was a significant decrease in gravid uterine weight in dams exposed to 200 ppm. There was no effect of exposure on hematologic parameters as observed in rats. For rats exposed to 200 ppm 2-butoxyethanol, the number of viable implants and percentage of live fetuses per litter were reduced. The number of nonviable implants, due to early resorptions, was increased. There were no significant increases in external, visceral, skeletal, or total malformations in the fetuses due to treatment. However, there was evidence of retarded skeletal ossification at 100 and 200 ppm. For rabbits, as with rats at 200 ppm 2-butoxyethanol, there was a significant reduction in the number of viable implants per litter; however, there was no effect of exposure on the number of nonviable implants. The authors concluded that exposure to 2-butoxyethanol resulted in maternal, embryonic, and fetal toxicity in rats at 100 or 200 ppm 2-butoxyethanol; maternal and embryonic toxicity in rabbits at 200 ppm; and no teratogenicity in rats or rabbits.

In a comparative developmental toxicity study, Hardin *et al*. (1984) tested five glycol ethers, including 2-butoxyethanol, administered to SPF Sprague-Dawley rats dermally. The original design was to test all five ethers at equimolar concentrations during gestation days 7 to 16; however, during the first replicate, 2-butoxyethanol at 0.35 mL was determined to be overtly toxic to the dams. In a subsequent replicate, the 2-butoxyethanol dose was reduced to 0.12 mL and, like the other glycol ethers, was administered four times a day (at 2.5 hour intervals) on gestation days 7 to 16. 2-Butoxyethanol at this dose caused no maternal toxicity, was not toxic to the embryo or fetus, and did not cause teratogenic effects. Diethylene glycol monoethyl ether (0.35 mL) caused a reduction in weight gain but, like 2-butoxyethanol, was not toxic to the embryo or fetus and was not teratogenic. 2-Ethoxyethanol (0.25) and ethylene glycol monoethyl ether acetate (0.35 mL) caused reduced weight gain in dams associated with completely resorbed litters and significantly fewer live fetuses per litter. Fetal body weights were reduced and visceral malformations and skeletal variations were increased when compared to controls.

Giavini *et al*. (1993) compared the embryotoxic potential of 2-butoxyethanol and 2-butoxyacetic acid, 2-ethoxyethanol and 2-ethoxyacetic acid and 2-methoxyethanol and 2-methoxyacetic acid in an *in vitro* system whereby 9.5-day-old embryos from CD rats were incubated with each glycol ether or alkoxy acetic acid for 48 hours. Final media concentrations for 2-butoxyethanol were 3.12, 6.25, 12.5, or 25 mM and for 2-butoxyacetic acid were 0.4, 0.8, 1.6, or 3.2 mM. For 2-butoxyethanol, embryonic development was blocked at 25 mM, and exposure to 12.5 mM 2-butoxyethanol resulted in

severe dysmorphogenic effects (inhibition of rotation and severe reduction of telencephalic vesicles). General embryotoxic effects, as shown by reduction of the somite number and of protein/embryo, were observed at 6.25 mM. There were no effects of 2-butoxyethanol at 3.12 mM. Incubation with 2-butoxyacetic acid resulted in abnormal embryos with morphologic alterations of brain vesicle size. Reduction in somite number and total protein/embryo was observed at all incubation concentrations of 2-butoxyacetic acid except at 0.4 mM 2-butoxyacetic acid, the no-effect level for all types of effects. Of importance is that in *in vitro* situations embryotoxicity increased with increased alkyl chain length of the glycol ether. 2-Butoxyethanol was more active than 2-ethoxyethanol, followed by 2-methoxyethanol, but the opposite was observed for the corresponding alkoxyacid; 2-methoxyacetic acid was more sensitive than 2-ethoxyacetic acid, followed by 2-butoxyacetic acid. Moreover, the embryotoxic potency of each acid was considerably higher than that of the corresponding ether.

In another study, Bowden *et al*. (1995) cultured 10-day-old Sprague-Dawley rat embryos for 48 hours with 2-butoxy-, 2-ethoxy-, or 2-methoxyethanol at media concentrations of 0.3, 0.5, 0.75, or 1.0 mg/mL. 2-Butoxyethanol caused marginal reduction in growth and developmental parameters at 0.3 mg/mL. At all doses, the embryos had poor yolk sac circulation, thin allantois, twisted flexion, incomplete fusion, and/or irregular formation of the caudal neural tube and brain, irregular posterior neuropore, and growth-retarded forelimb buds. At 1.0 mg/mL, five of 10 embryos died. As reported by Giavani *et al*. (1993), embryo toxicity was directly related to increased alkyl chain length of the glycol ether (2-butoxyethanol was more active than 2-ethoxyethanol, followed by 2-methoxyethanol). The results of embryo culture with glycol ethers were the opposite of what was observed in inhalation and dermal *in vivo* rat studies, in which embryo toxicity was directly related to decreased chain length of glycol ethers; 2-methoxyethanol was more active than 2-ethoxyethanol, followed by 2-butoxyethanol (Hardin *et al*., 1984; Nelson *et al*., 1984), which may be because the glycol ethers are rapidly metabolized to the alkoxyacids *in vivo*.

Humans

No information on the reproductive or developmental toxicity of 2-butoxyethanol in humans was found in the available literature.

CARCINOGENICITY

No information on the carcinogenicity of 2-butoxyethanol in experimental animals was found in the available literature; additionally, no epidemiologic studies or case reports examining the relationship between exposure to 2-butoxyethanol and cancer in humans were found in the literature.

GENETIC TOXICITY

Published information on the genotoxicity of 2-butoxyethanol, recently reviewed by Elliot and Ashby (1997), indicates that the chemical is not mutagenic, consistent with the absence of structural alerts to genotoxicity (Tennant and Ashby, 1991). Results of *Salmonella typhimurium* gene mutation assays with 2-butoxyethanol were negative in the presence and in the absence of induced hamster or rat liver S9 (Zeiger *et al.*, 1992). Positive results were reported (Hoflack *et al.*, 1995) with 2-butoxyethanol in a later *S. typhimurim* test with strain TA97a [closely related to TA97, which was used in the Zeiger *et al.* (1992) study and shows the same response as TA97 to mutagens that produce frameshift alterations], but an independent replication of the study using a well-characterized sample of 2-butoxyethanol was unable to duplicate the positive response (Gollapudi *et al.*, 1996). In addition, Gollapudi *et al.* (1996) tested 2-butoxyethanol for mutagenicity in TA100 and in *Escherichia coli* WP2 uvrA, and no mutagenic activity was detected. 2-Butoxyethanol did not induce gene mutations in cultured Chinese hamster ovary AS52 cells in the absence of S9 activation and a major metabolite of 2-butoxyethanol, 2-butoxyacetaldehyde, also gave negative results in this assay (Chiewchanwit and Au, 1995).

Keith *et al*. (1996) reported that no increase in DNA adducts was detected by ^{32}P postlabeling in the brain, liver, kidney, testis, or spleen of Sprague-Dawley rats following oral administration of 120 mg/kg 2-butoxyethanol. No increases in the frequencies of

sister chromatid exchanges or micronucleated lymphocytes were observed in peripheral blood lymphocytes of varnish plant workers exposed to 2-butoxyethanol and other glycol ethers (Söhnlein *et al.*, 1993).

In summary, 2-butoxyethanol was not mutagenic in bacterial or mammalian cells *in vitro*, and no evidence of DNA damage was detected *in vivo* in rats or in exposed workers. This data set is limited, but all evidence supports the conclusion that 2-butoxyethanol is nonmutagenic.

STUDY RATIONALE

The Consumer Product Safety Commission and the United Auto Workers International Union nominated 2-butoxyethanol for study because of its widespread use in industrial and consumer applications, the potential for exposure to workers and the general population, and the absence of chronic toxicity data. Inhalation was chosen as the route of exposure because human exposure occurs primarily by this route.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2-BUTOXYETHANOL

2-Butoxyethanol was obtained from Dow Chemical U.S.A. (Plaquemine, LA) in two lots. Lot QP-911021-26D1 was used during the 14-week studies, and lot QP-921215-26D2 was used during the 2-year studies. Identity and purity analyses were conducted by the study laboratory. Reports on analyses performed in support of the 2-butoxyethanol studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a clear, colorless liquid, were identified as 2-butoxyethanol by infrared and nuclear magnetic resonance (proton and C^{13}) spectroscopy. The infrared spectrum was consistent with that expected for the structure, with the literature spectra (*Aldrich*, 1981, 1983), and/or with those of a reference sample obtained from Aldrich Chemical Company (Milwaukee, WI). Purity of each lot was determined by elemental analysis, Karl Fischer water analysis, titrations for acid and peroxide content, and gas chromatography with flame ionization detection. For both lots, elemental analyses for carbon, hydrogen, and oxygen were in agreement with the theoretical values for 2-butoxyethanol. Karl Fischer water analysis indicated 0.02% water for lot QP-911021-26D1 and 0.0254% water for lot QP-921215-26D2. Titrations indicated 0.001% acidity (as acetic acid) and 105 ppm peroxide for lot QP-911021-26D1, well within the acceptable limits of 0.02% acid and 5,000 ppm peroxide; titrations indicated less than 0.003% acetic acid and less than 1,000 ppm peroxide for lot QP-921215-26D2.

Gas chromatographic analysis of lot QP-911021-26D1 indicated one major peak and one impurity with an area of 0.1% relative to the major peak area. Gas chromatographic analysis of lot QP-921215-26D2 indicated one major peak and three impurities with areas greater than 0.1% of the major peak area; these impurities were tentatively identified as ethylene glycol, 2-ethyl-2-hexenal, and 2-ethyl-1-hexanol by gas chromatography/mass spectroscopy with electron impact ionization detection. Major peak comparisons of each lot relative to a reference sample were performed by gas chromatography; results indicated a purity of 100.8% for lot QP-911021-26D1 and 99.2% for lot QP-921215-26D2 relative to the reference sample. The overall purity of each lot was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by Midwest Research Institute (MRI, Kansas City, MO) (MRI, 1984). These studies indicated that 2-butoxyethanol is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature during the 14-week studies and at approximately 16° C during the 2-year studies in stainless steel containers. Throughout the studies, stability was monitored by titrations for acid and peroxide and by gas chromatography with flame ionization detection. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

2-Butoxyethanol was held in a stainless-steel reservoir under a nitrogen blanket. A liquid micrometering pump was used to pump 2-butoxyethanol into a glass column filled with glass beads and heated by flexible electric heat tape encircling the column. Vapor temperature was monitored at the top of the condenser column by a temperature sensor. The total output of the generator was calculated from the metered nitrogen flow and the 2-butoxyethanol vapor pressure at the exit temperature.

To prevent 2-butoxyethanol from condensing while in transport to the exposure room, the Teflon® transport line was heated. The vapor was mixed with heated HEPA- and charcoal-filtered air before entering a short vapor distribution manifold. An automatic

controller maintained a constant flow in the distribution manifold.

Compressed-air pumps delivered the vapor from the distribution manifold to the exposure chambers via individual temperature-controlled Teflon® delivery lines. A three-way valve between the distribution line and each chamber directed vapor to the exposure chamber exhaust until a stable concentration of 2-butoxyethanol vapor was collected in the distribution line. At each chamber, the vapor was further diluted with conditioned, HEPA- and charcoal-filtered chamber air to the appropriate 2-butoxyethanol concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small-particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that 2-butoxyethanol vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

PILOT STUDIES

Pilot studies were conducted to determine the maximum concentration of 2-butoxyethanol vapor that could be generated without the presence of 2-butoxyethanol aerosols and to determine the acute toxicity of 2-butoxyethanol in male and female rats and mice at those concentrations. Aerosols were generated at approximately 800 ppm; 4-week-old F344/N rats and $B6C3F_1$ mice were exposed to 31 to 700 ppm 2-butoxyethanol by inhalation for 3 to 14 days.

VAPOR CONCENTRATION MONITORING

Chamber concentrations of 2-butoxyethanol were monitored with an on-line gas chromatograph. Samples were drawn from each chamber approximately every 16 minutes (14-week studies) or 30 minutes (2-year studies) during exposures by a computer-controlled, 12-port, stream select valve. The on-line gas chromatograph was calibrated by a comparison of chamber concentration data to data from grab samples analyzed by an off-line gas chromatograph; the grab samples were collected in bubblers containing water. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of 2-butoxyethanol during the 14-week and 2-year studies. Summaries of the chamber concentrations for the 14-week and 2-year studies are in Tables H2 and H3.

CHAMBER ATMOSPHERE CHARACTERIZATION

At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. Prior to and during the 14-week and 2-year studies, T_{90} and T_{10} ranges were determined with and without animals. A T_{90} value of 12 minutes was selected for all studies.

Studies of 2-butoxyethanol degradation and monitoring for impurities were conducted throughout the studies by gas chromatography; chamber concentration uniformity was maintained throughout the 14-week and 2-year studies, and no significant degradation of 2-butoxyethanol was observed.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 2-butoxyethanol and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 11 or 12 days and were 6 weeks old on the first day of the studies. Before initiation of the studies, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. Serologic analyses were performed on five male and five female sentinel rats and mice on day 10 and on five male and

five female control rats and mice at the end of the studies using the protocols of the NTP Sentinel Animal Program (Appendix J).

Groups of 10 male and 10 female rats and mice were exposed to 2-butoxyethanol at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Rats and mice were housed individually. Animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded weekly and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 14-week studies, rats and mice were anesthetized with a CO_2:O_2 mixture, and blood was collected from the retroorbital sinus for hematology analyses and placed in tubes containing potassium EDTA as the anticoagulant. Hematology determinations, including erythrocyte, leukocyte, and platelet counts, hemoglobin concentration, packed cell volume, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration, were performed on an Ortho ELT-8/ds 9000 hematology analyzer (Ortho Diagnostic Systems, Westwood, MA). Hematocrit was also determined manually using a Damon/IEC microcapillary centrifuge and reader (International Equipment Company, Needham Heights, MA). Leukocyte differential and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright's stain on a Wescor Stainer (Wescor, Logan, UT). Smears made from preparations of equal volumes of new methylene blue and whole blood and incubated at room temperature for 20 minutes were examined microscopically, using the Miller disc method, for the quantitative determination of reticulocytes.

A necropsy was performed on all animals. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on chamber control and 500 ppm rats and mice and on 250 ppm female rats. Target organs were identified and evaluated to a no-observable-adverse-effect level. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were exposed to 2-butoxyethanol by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 104 weeks. Rats were exposed to 0, 31.2, 62.5, or 125 ppm, and mice were exposed to 0, 62.5, 125, or 250 ppm.

For hematology and bone marrow analyses, additional groups of 27 male and 27 female rats were exposed to 0, 62.5, or 125 ppm 2-butoxyethanol, nine male and nine female rats were exposed to 31.2 ppm 2-butoxyethanol, and 30 male and 30 female mice were exposed to 0, 62.5, 125, or 250 ppm 2-butoxyethanol. Nine male and nine female rats exposed to 0, 62.5, or 125 ppm 2-butoxyethanol and 10 male and 10 female mice from each exposure group were evaluated at 3, 6, or 12 months; nine male and nine female rats exposed to 31.2 ppm 2-butoxyethanol were evaluated at 3 (hematology only) and 6 months.

Source and Specification of Animals

Male and female F344/N rats and B6C3F_1 mice were obtained from Taconic Laboratory Animals and Services for use in the 2-year studies. Rats and mice were quarantined for 18 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were 7 to 8 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Rats and mice were housed individually. Water was available *ad libitum*; feed was available *ad libitum* except during exposure periods. Cages were rotated weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix I.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially; body weights and clinical findings were recorded monthly from week 5 through week 89 (rats) or week 93 (mice) and every 2 weeks from week 92 (rats) or week 94 (mice) until the end of the studies.

At 3, 6, and 12 months, the rats and mice selected as part of the hematology studies were anesthetized with a CO_2:O_2 mixture, and blood was collected from the retroorbital plexus and placed in tubes containing potassium EDTA as the anticoagulant. As in the 14-week studies, 3- and 6-month hematology determinations were performed on an Ortho ELT-8/ds 9000 hematology analyzer; a Roche COBAS Helios analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ) was used at 12 months. Leukocyte differential and nucleated erythrocyte counts were determined by light microscopic examination of blood films stained with Wright's stain using a Wescor Stainer. Bone marrow samples were taken by flushing the cells from the femur into tubes containing tissue culture media. Marrow cellularity was enumerated using a hydrodynamically focused electronic impedance system (Coulter Model Z_H, Coulter Electronics, Inc., Hialeah, FL). Cytological evaluations of bone marrow cell morphology and myeloid/erythroid ratios were performed by microscopic examination of Wright's-stained, cytocentrifuged preparations from bone marrow samples collected for cellularity counts. Hematology and bone marrow cellularity parameters measured are listed in Table 1.

Complete necropsies and microscopic examinations were performed on all core study rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the bone marrow, forestomach, kidney, liver, lung, nose, and spleen of all male and female rats and mice; the adrenal gland and clitoral gland of female rats; and the preputial gland, prostate gland, skin (prepuce), testis, and urinary bladder of male mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

Toxicokinetic Studies

The study design and results of toxicokinetic studies conducted utilizing special study rats and mice during the 2-year studies are provided in Dill *et al.* (1998) and Lee *et al.* (1998).

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

14-Week Studies	2-Year Studies
Study Laboratory Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies 11 days (males) or 12 days (females)	18 days
Average Age When Studies Began 6 weeks	Rats: 7-8 weeks Mice: 7 weeks
Date of First Exposure 23 (males) or 24 (females) March 1992	Rats: 23 August 1993 Mice: 26 July 1993
Duration of Exposure 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 14 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 weeks
Date of Last Exposure Rats: 22 (males) or 23 (females) June 1992 Mice: 24 (males) or 25 (females) June 1992	Rats: 18 August 1995 Mice: 21 July 1995
Necropsy Dates Rats: 23 (males) or 24 (females) June 1992 Mice: 25 (males) or 26 (females) June 1992	Rats: 21-23 August 1995 Mice: 24-28 July 1995
Average Age at Necropsy 19 weeks	Rats: 111-112 weeks Mice: 111 weeks
Size of Study Groups 10 males and 10 females	Core study: 50 males and 50 females Hematology and bone marrow analyses: Rats: 27 males and 27 females (0, 62.5, or 125 ppm), or 9 males and 9 females (31.2 ppm) Mice: 30 males and 30 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weight.	Same as 14-week studies
Animals per Cage 1	1
Method of Animal Identification Tail tattoo	Tail tattoo

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

14-Week Studies	2-Year Studies
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods; changed weekly	Same as 14-week studies
Water Tap water (City of Richland municipal supply) softened at Battelle and delivered via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 14-week studies
Cages Stainless steel wire-bottom cages (Hazleton Systems, Inc., Aberdeen, MD), changed weekly	Same as 14-week studies
Chamber Air Supply Filters Single HEPA (Northland Filter Systems International, Mechanicville, NY) and charcoal (RSE, Inc., New Baltimore, MI)	Single HEPA (Flanders Filters, Inc., San Rafael, CA) and purafil (Environmental Systems, Lynnwood, WA)
Chambers Stainless steel chambers (Lab Products, Inc., Harford System Division, Aberdeen, MD), changed weekly	Same as 14-week studies
Chamber Environment Temperature: 23.9°-24.3° C Relative humidity: 55%-56% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 23.7°-24.1° C (rats) or 24.0°-24.3° C (mice) Relative humidity: 57%-58% (rats) or 54%-56% (mice) Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations 0, 31, 62.5, 125, 250, or 500 ppm	Rats: 0, 31.2, 62.5, or 125 ppm Mice: 0, 62.5, 125, or 250 ppm
Type and Frequency of Observation Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded weekly and at the end of the studies.	Observed twice daily; animals were weighed initially and body weights and clinical findings were recorded monthly from week 5 through week 89 (rats) or week 93 (mice) and every 2 weeks from week 92 (rats) or week 94 (mice) until the end of the studies.
Method of Sacrifice Asphyxiation with 70% CO_2	Asphyxiation with 70% CO_2
Necropsy Necropsy performed on all animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on core study animals.

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

14-Week Studies	2-Year Studies
Clinical Pathology	
Blood was collected from the retroorbital sinus of all animals surviving to the end of the studies for hematology analyses. ***Hematology:*** automated hematocrit; manual hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; total leukocyte count and differentials; and morphologic assessment of erythrocytes, platelets, and leukocytes	Blood was collected from the retroorbital plexus of nine male and nine female rats and 10 male and 10 female mice designated for hematology analyses at 3, 6, and/or 12 months (except 31.2 ppm rats). Femurs were collected from these same animals for bone marrow analyses. ***Hematology:*** automated hematocrit; manual hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; total leukocyte count and differentials; and morphologic assessment of erythrocytes, platelets, and leukocytes ***Bone Marrow:*** total nucleated bone marrow cell count and myeloid/ erythroid ratio
Histopathology	
Complete histopathology was performed on 0 and 500 ppm rats, 250 ppm female rats, and 0 and 500 ppm mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder and uterus. In addition, the bone marrow, forestomach, kidney, liver, and spleen of male rats; nose, salivary gland, tail, and thymus of female rats; and the kidney, liver, lung, lymph nodes (mandibular and mesenteric), stomach, testis, and thymus of male and female mice were examined at all other exposure levels.	Complete histopathology was performed on all core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues

(e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1-P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Blood and bone marrow hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated

yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of 2-butoxyethanol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in bone marrow of male rats and mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of 2-butoxyethanol are part of a larger effort by the NTP to develop a comprehensive database that would permit a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). These short-term genetic toxicity tests were originally developed to clarify mechanisms of chemical-induced DNA damage growing out of the earlier electrophilicity/mutagenicity relationship proposed by (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). Therefore, the information obtained from these tests applies only to mutagenic carcinogens.

For mutagenic carcinogens, there is a strong correlation between a chemical's potential for DNA reactivity, mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of DNA reactivity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in multiple species and genders of rodents and at multiple tissue sites (Ashby and Tennant, 1991). Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) and that there is no complementarity among the *in vitro* genetic toxicity tests (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. Although other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity compared with the *Salmonella* test, these other tests can provide useful information on the types of DNA and chromosomal effects induced by the chemical under investigation.

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

RESULTS

RATS

14-WEEK STUDY

Six female rats were killed moribund during the study. One female rat in the 250 ppm group was killed moribund during week 8; four females in the 500 ppm group were killed moribund during week 1 and one during week 5 (Table 2). All other animals survived to the end of the study. The final mean body weights and body weight gains of females exposed to 500 ppm were significantly less than those of the chamber controls. Clinical findings were most prevalent in rats exposed to 125, 250, or 500 ppm and included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy, and increased salivation and/or lacrimation. In addition, all females exposed to 500 ppm displayed tail lesions consisting of alternating bands of dark purplish blue with blanched white bands in approximately the distal one-third of the tail. This progressed to self-mutilation (chewing off) and/or sloughing of this portion of the tail. These findings were most prevalent during the first 2 weeks of the study; however, all females exposed to 500 ppm lost the distal portion of the tail.

TABLE 2
Survival and Body Weights of Rats in the 14-Week Inhalation Study of 2-Butoxyethanol

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	132 ± 2	355 ± 7	223 ± 7	
31	10/10	128 ± 4	364 ± 6	235 ± 4	103
62.5	10/10	132 ± 3	367 ± 3	235 ± 3	103
125	10/10	130 ± 3	346 ± 8	217 ± 8	97
250	10/10	129 ± 2	349 ± 6	220 ± 5	98
500	10/10	132 ± 2	357 ± 5	225 ± 5	101
Female					
0	10/10	112 ± 2	217 ± 5	105 ± 4	
31	10/10	112 ± 2	211 ± 3	99 ± 2	97
62.5	10/10	111 ± 2	206 ± 4	95 ± 3	95
125	10/10	111 ± 1	211 ± 4	100 ± 3	97
250	9/10[c]	111 ± 2	210 ± 7	99 ± 5	97
500	5/10[d]	110 ± 2	197 ± 4*	89 ± 3*	91

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 8
[d] Week of death: 1, 1, 1, 1, 5

The hematology data are listed in Tables 3 and F1. An exposure concentration-related anemia, evidenced by decreases in automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in the 125 ppm or greater males and all exposed groups of females. Females appeared to be slightly more sensitive to 2-butoxyethanol than males. Besides the anemia in all exposed female groups, the gender difference was evidenced by approximately 25% to 35% decreases in hematocrit value and hemoglobin concentration and a 44% decrease in erythrocyte count for the 500 ppm females compared to approximately 20% to 25% decreases in hematocrit value and hemoglobin concentration and a 34% decrease in erythrocyte count for the 500 ppm males. The anemia was characterized as macrocytic, normochromic, and responsive. Evidence of macrocytosis was demonstrated by increases in the mean cell volumes, which occurred in males exposed to 125 ppm or greater and females exposed to 62.5 ppm or greater. Increased mean cell hemoglobin values occurred concurrently with the increased mean cell volumes. Normochromic erythrocytes were evidenced by the lack of change in the mean cell hemoglobin concentrations. Evidence of an erythropoietic response was demonstrated by increases in the reticulocyte and nucleated erythrocyte counts which occurred in males exposed to 125 ppm or greater and females exposed to 62.5 ppm or greater.

Microscopic evaluation of blood smears of rats in the 500 ppm groups revealed increased numbers of polychromatophilic erythrocytes; occasional microcytes also were observed. Decreases in leukocyte counts, characterized by decreased lymphocyte and monocyte counts, occurred in males exposed to 125 ppm or greater. Platelet counts increased in females exposed to 125 or 500 ppm.

TABLE 3
Selected Hematology Data for Rats in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Male						
n	10	10	10	10	10	10
Automated hematocrit (mL/dL)	45.5 ± 0.4	43.8 ± 0.7	45.1 ± 0.4	42.7 ± 0.5**	38.4 ± 0.4**	34.9 ± 0.3**
Manual hematocrit (%)	46.8 ± 0.5	45.8 ± 0.6	47.0 ± 0.4	44.5 ± 0.5**	41.1 ± 0.3**	37.3 ± 0.4**
Hemoglobin (g/dL)	15.5 ± 0.1	14.8 ± 0.3	15.4 ± 0.1	14.5 ± 0.2**	13.1 ± 0.1**	11.7 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.05 ± 0.08	8.71 ± 0.14*	8.91 ± 0.06	8.01 ± 0.08**	7.10 ± 0.07**	5.97 ± 0.05**
Reticulocytes ($10^6/\mu L$)	0.16 ± 0.02	0.17 ± 0.03	0.15 ± 0.02	0.30 ± 0.04**	0.48 ± 0.06**	0.68 ± 0.07**
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.01	0.04 ± 0.03	0.11 ± 0.03	0.17 ± 0.04**	0.20 ± 0.06*
Mean cell volume (fL)	50.4 ± 0.3	50.2 ± 0.2	50.7 ± 0.2	53.1 ± 0.2**	53.8 ± 0.3**	58.5 ± 0.3**
Mean cell hemoglobin (pg)	17.1 ± 0.1	17.0 ± 0.1	17.3 ± 0.1	18.1 ± 0.1**	18.4 ± 0.1**	19.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.9 ± 0.2	33.7 ± 0.2	34.2 ± 0.2	33.9 ± 0.1	34.1 ± 0.2	33.4 ± 0.1
Leukocytes ($10^3/\mu L$)	6.70 ± 0.29	6.29 ± 0.38	6.13 ± 0.33	5.87 ± 0.24*	5.72 ± 0.36*	5.34 ± 0.17**
Lymphocytes ($10^3/\mu L$)	5.34 ± 0.26	4.99 ± 0.33	4.82 ± 0.28	4.72 ± 0.22	4.65 ± 0.20*	3.93 ± 0.42**
Monocytes ($10^3/\mu L$)	0.19 ± 0.04	0.19 ± 0.05	0.11 ± 0.03	0.08 ± 0.02*	0.06 ± 0.02**	0.08 ± 0.04*
Female						
n	10	10	10	10	9	5
Automated hematocrit (mL/dL)	46.7 ± 0.3	44.7 ± 0.5**	43.6 ± 0.5**	40.5 ± 0.3**	37.4 ± 0.3**	31.9 ± 0.6**
Manual hematocrit (%)	48.5 ± 0.5	46.0 ± 0.5**	45.2 ± 0.5**	42.9 ± 0.4**	40.0 ± 0.3**	36.2 ± 0.6**
Hemoglobin (g/dL)	15.6 ± 0.1	15.0 ± 0.1**	14.6 ± 0.1**	13.6 ± 0.1**	12.5 ± 0.1**	10.5 ± 0.3**
Erythrocytes ($10^6/\mu L$)	8.48 ± 0.05	8.08 ± 0.07**	7.70 ± 0.08**	6.91 ± 0.05**	6.07 ± 0.04**	4.77 ± 0.15**
Reticulocytes ($10^6/\mu L$)	0.13 ± 0.02	0.10 ± 0.01	0.16 ± 0.02	0.26 ± 0.04*	0.34 ± 0.04**	0.40 ± 0.11**
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.02	0.12 ± 0.03*	0.18 ± 0.07	0.61 ± 0.24**	0.73 ± 0.27**
Mean cell volume (fL)	55.1 ± 0.3	55.3 ± 0.2	56.4 ± 0.2**	58.7 ± 0.2**	61.6 ± 0.2**	66.8 ± 0.9**
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.6 ± 0.2	19.0 ± 0.0**	19.6 ± 0.1**	20.6 ± 0.1**	22.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.1	33.6 ± 0.3	33.6 ± 0.1	33.6 ± 0.2	33.4 ± 0.1	32.9 ± 0.2
Platelets ($10^3/\mu L$)	573.5 ± 19.5	576.1 ± 31.6	583.5 ± 13.3	657.0 ± 25.7*	611.6 ± 25.6	719.6 ± 52.9*

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

Kidney weights of males exposed to 500 ppm and females exposed to 125 ppm or greater and liver weights of males exposed to 250 or 500 ppm and females exposed to 125 ppm or greater were significantly greater than those of the chamber controls (Table G1). Thymus weights of females exposed to 500 ppm were significantly less.

Female rats that were killed moribund during the study exhibited a number of histopathologic changes (Table 4). Thrombosis occurred in a number of tissues in females exposed to 500 ppm. The thrombosis was associated with areas of infarction in the tail and necrosis in the incisors and liver. Thrombosis was present in the atrium of the heart, in the blood

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Female Rats Killed Moribund in the 14-Week Inhalation Study of 2-Butoxyethanol

	250 ppm		500 ppm	
Tail, Vertebrae[a]	1		5	
Thrombosis[b]	0		4	(2.0)[c]
Infarct	0		5	(3.0)
Bone Marrow, Necrosis	0		5	(2.0)
Femur	1		3	
Thrombosis	0		2	(1.0)
Bone Marrow, Hyperplasia	1	(2.0)	1	(2.0)
Tooth, Incisor	1		5	
Dental Pulp, Thrombosis	0		4	(2.0)
Odontoblast, Degeneration	0		4	(2.0)
Nasal Cavity	1		5	
Thrombosis	0		3	(2.0)
Lung	1		5	
Thrombosis	0		3	(1.0)
Heart, Atrium	1		5	
Thrombosis	0		1	(2.0)
Forestomach	1		5	
Inflammation	0		3	(1.7)
Necrosis	0		2	(1.5)
Ulcer	0		2	(2.0)
Hyperplasia	0		1	(1.0)
Liver	1		5	
Necrosis	1	(1.0)	4	(2.0)
Thrombosis	0		3	(1.0)
Centrilobular, Degeneration	0		4	(2.0)
Kupffer Cell, Pigmentation	1	(1.0)	1	(1.0)
Kidney, Renal Tubule	1		5	
Degeneration	0		4	(2.0)
Pigmentation	1	(1.0)	2	(1.0)
Spleen	1		5	
Atrophy	0		1	(2.0)
Hematopoietic Cell Proliferation	0		2	(1.5)
Thymus	1		5	
Atrophy	0		4	(2.5)

[a] Number of animals killed moribund
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

vessels of the lamina propria of the nasal septum of the most anterior nasal section (Plate 1), in central veins of the liver associated with large foci of necrosis, in the lung, and in blood vessels of the dental pulp (Plates 2 and 3), which was associated with focal odontoblast degeneration. In addition, thrombi were noted within the metaphyseal vessels of the femur and the intramedullary and periosteal blood vessels in the vertebrae of the tail. There were also areas of necrosis within the marrow. The remaining portion of the tails in these females had infarcts in the cortical and trabecular bone of the coccygeal vertebrae (Plate 4). This was also noted in females surviving to the end of the study. Many of the osteocytes within the cortical and especially the trabecular bone exhibited nuclear pyknosis/ fragmentation to complete loss of nuclear staining, often appearing as ghost cells. Growth plate and articular chondrocytes also exhibited loss of nuclear staining consistent with cell death. In the female rat that was killed moribund on day 32, there were additional changes noted in the coccygeal vertebrae. These included necrosis of the marrow (including adipocytes) and the presence of growth arrest lines. On the growth plate side of the growth arrest lines, there was no evidence of necrosis; however, on the diaphyseal side of the growth arrest lines, there was evidence of widespread marrow and bone infarction. The longitudinal growth in the area of infarction was reduced or completely stopped and was associated with growth plate degenerative changes. Affected marrow was infiltrated by macrophages (foreign body type inflammation) in response to fat necrosis.

In the tail vertebrae of female rats in the 500 ppm group that were killed at the end of the study, there were lesions consistent with prior infarction with transient or complete growth arrest. In the most severely affected vertebrae, there was growth plate degeneration with no evidence of renewed longitudinal growth, indicating irreversible growth plate injury. These vertebrae exhibited marrow necrosis that extended to the growth plate, capping of the growth plate with a dense layer of bone, and degeneration of the growth plate cartilage. In other vertebrae, renewed longitudinal growth was evidenced by the presence of growth arrest lines. The presence of a single growth arrest line at the end of each vertebra is consistent with a single ischemic insult, and its presence also confirmed renewed longitudinal growth which could only occur if blood flow was normalized after the insult. The space between the arrest line and growth plate represents the period of time between resuming longitudinal growth and terminal sacrifice.

Also observed in rats killed moribund during the study were atrophy of the spleen and thymus, characterized by depletion of lymphocytes from the white pulp of the spleen and from the cortex of the thymus; inflammation, necrosis, ulceration, and hyperplasia of the forestomach; centrilobular degeneration of the liver characterized by fatty change, presence of granular eosinophilic debris, single cell necrosis, and some neutrophil infiltration; and renal tubule degeneration in which the affected tubules, located mainly in the cortex, had dilated lumens with flattened and/or necrotic epithelium. The luminal contents of the tubules stained intensely red and in some tubules resembled crystalline hemoglobin. Renal changes are consistent with a hemoglobinuric nephrosis.

The histopathologic lesions noted in rats at terminal sacrifice were similar between males and females and were consistent with hemolytic anemia and hemoglobinuria (Table 5). Many of these effects were the same as those observed in females killed moribund during the study. Minimal hematopoietic cell proliferation of the spleen, primarily erythroid, was noted in female rats exposed to 62.5 ppm or greater and in male rats exposed to 250 ppm or greater compared to the chamber controls. The incidences of bone marrow hyperplasia in males exposed to 250 ppm or greater and in females exposed to 62.5 ppm or greater were significantly increased. An exposure concentration-related increase in the incidence of pigmentation of the hepatic Kupffer cells was noted in males and females exposed to 125 ppm or greater and in the females exposed to 62.5 ppm. In addition, there was a concentration-related deposition of pigment in the renal cortical tubules in males and females exposed to 250 or 500 ppm and in 125 ppm females. Liver and kidney pigmentation stained positive for Perls' Prussian blue stain for iron, which is consistent with hemosiderin. Minimal forestomach inflammation and epithelial hyperplasia were noted in male rats exposed to 250 or 500 ppm. In addition, one female exposed to 250 ppm and one female exposed to 500 ppm had epithelial hyperplasia of the forestomach.

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats at Terminal Sacrifice in the 14-Week Inhalation Study of 2-Butoxyethanol

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Male						
Liver[a]	10	10	10	10	10	10
Kupffer Cell, Pigmentation[b]	0	0	0	7** (1.0)[c]	10** (1.0)	10** (1.0)
Bone Marrow	10	10	10	10	10	10
Hyperplasia	0	0	0	0	10** (1.7)	10** (2.7)
Spleen	10	10	10	10	10	10
Hematopoietic Cell Proliferation	0	1 (1.0)	0	0	10** (1.0)	10** (1.0)
Kidney	10	10	10	10	10	10
Renal Tubule, Pigmentation	0	0	0	0	8** (1.0)	10** (1.0)
Forestomach	10	10	10	10	10	10
Inflammation	0	0	0	0	2 (1.0)	2 (1.0)
Epithelium, Hyperplasia	0	0	0	0	3 (1.7)	2 (1.0)
Female						
Tail, Vertebrae	10	10	10	10	9	5
Infarct	0	0	0	0	0	5** (3.0)
Bone Marrow, Necrosis	0	0	0	0	0	5** (2.0)
Liver	10	10	10	10	9	5
Kupffer Cell, Pigmentation	0	0	10** (1.0)	10** (1.0)	9** (1.0)	5** (1.0)
Bone Marrow	10	10	10	10	9	5
Hyperplasia	0	0	8** (1.0)	10** (2.0)	9** (2.5)	5** (3.0)
Spleen	10	10	10	10	9	5
Hematopoietic Cell Proliferation	0	0	1 (1.0)	10** (1.0)	8** (1.0)	5** (1.4)
Kidney	10	10	10	10	9	5
Renal Tubule, Pigmentation	0	0	0	10** (1.0)	9** (1.0)	5** (1.0)
Forestomach	10	10	10	10	9	5
Epithelium, Hyperplasia	0	0	0	0	1 (1.0)	1 (1.0)

** Significantly different ($P \leq 0.01$) from the chamber control group by the Fisher exact test
[a] Number of animals examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Exposure Concentration Selection Rationale: The hematologic effects in rats exposed to 125 ppm were not considered sufficiently severe to preclude the use of this concentration in a 2-year study. In addition, 62.5 ppm was a no-effect concentration for male rats, and in females the overall change in erythrocyte cell indices was less than 10% from the chamber controls. Based on the hematologic effects, 2-butoxyethanol exposure concentrations selected for the 2-year inhalation study in rats were 31.2, 62.5, and 125 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 2). Survival of exposed male and female rats was similar to the chamber control groups.

Body Weights and Clinical Findings

Mean body weights of all exposed groups of males and of females exposed to 31.2 or 62.5 ppm were generally similar to those of the chamber controls (Figure 3; Tables 7 and 8). The mean body weights of females exposed to 125 ppm were generally less than those of the chamber control groups from week 17 until the end of the study. No clinical findings were attributed to 2-butoxyethanol exposure.

TABLE 6
Survival of Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	25	31	24	21
Natural deaths	6	8	5	5
Animals surviving to study termination	19	11	21	24
Percent probability of survival at end of study[a]	38	22	42	48
Mean survival (days)[b]	660	650	654	669
Survival analysis[c]	P=0.115N	P=0.196	P=0.772N	P=0.393N
Female				
Animals initially in study	50	50	50	50
Moribund	18	21	23	26
Natural deaths	3	2	4	3
Animals surviving to study termination	29	27	23	21
Percent probability of survival at end of study	58	54	46	42
Mean survival (days)	688	689	660	678
Survival analysis	P=0.106	P=0.832	P=0.238	P=0.159

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

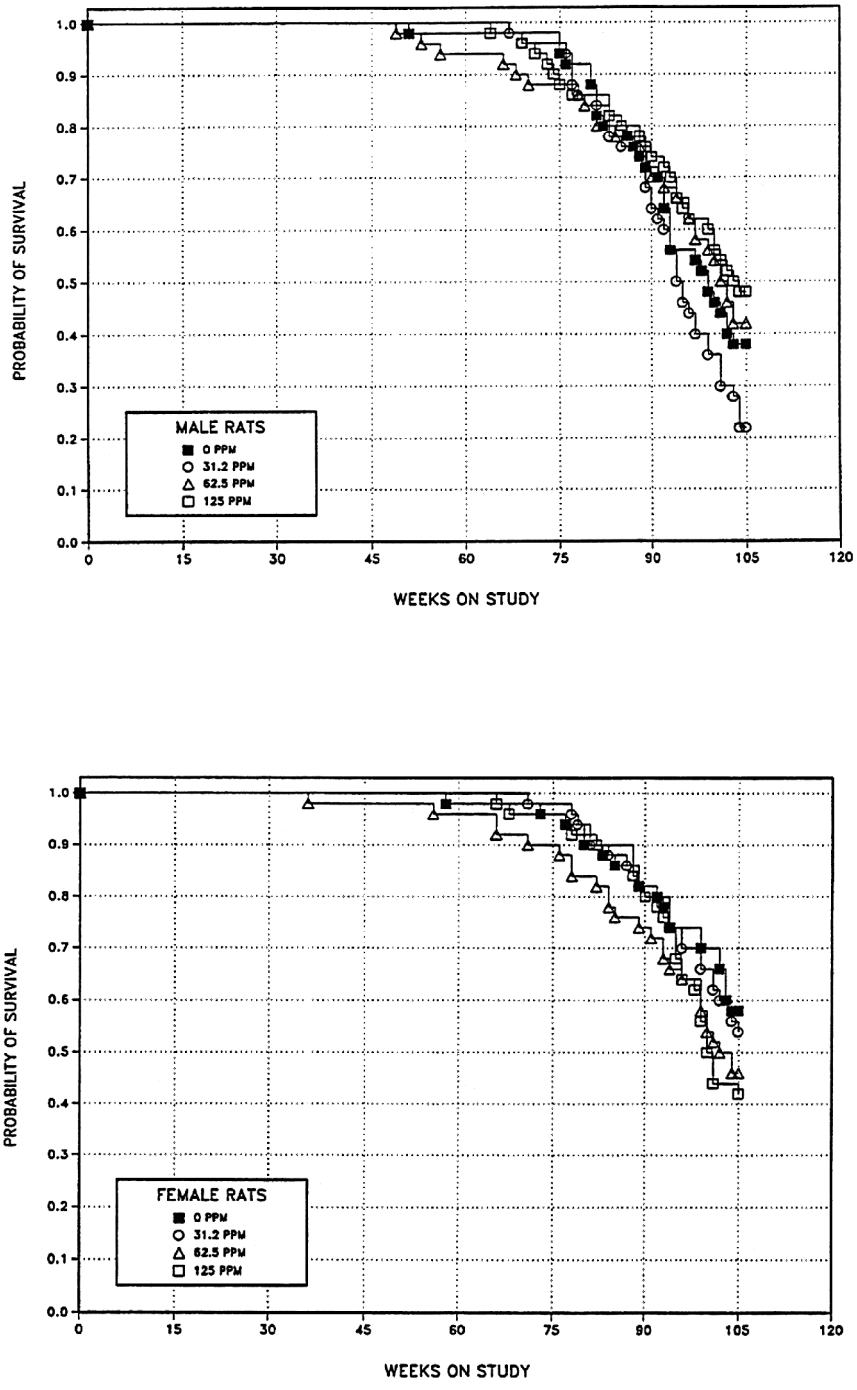

FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to 2-Butoxyethanol by Inhalation for 2 Years

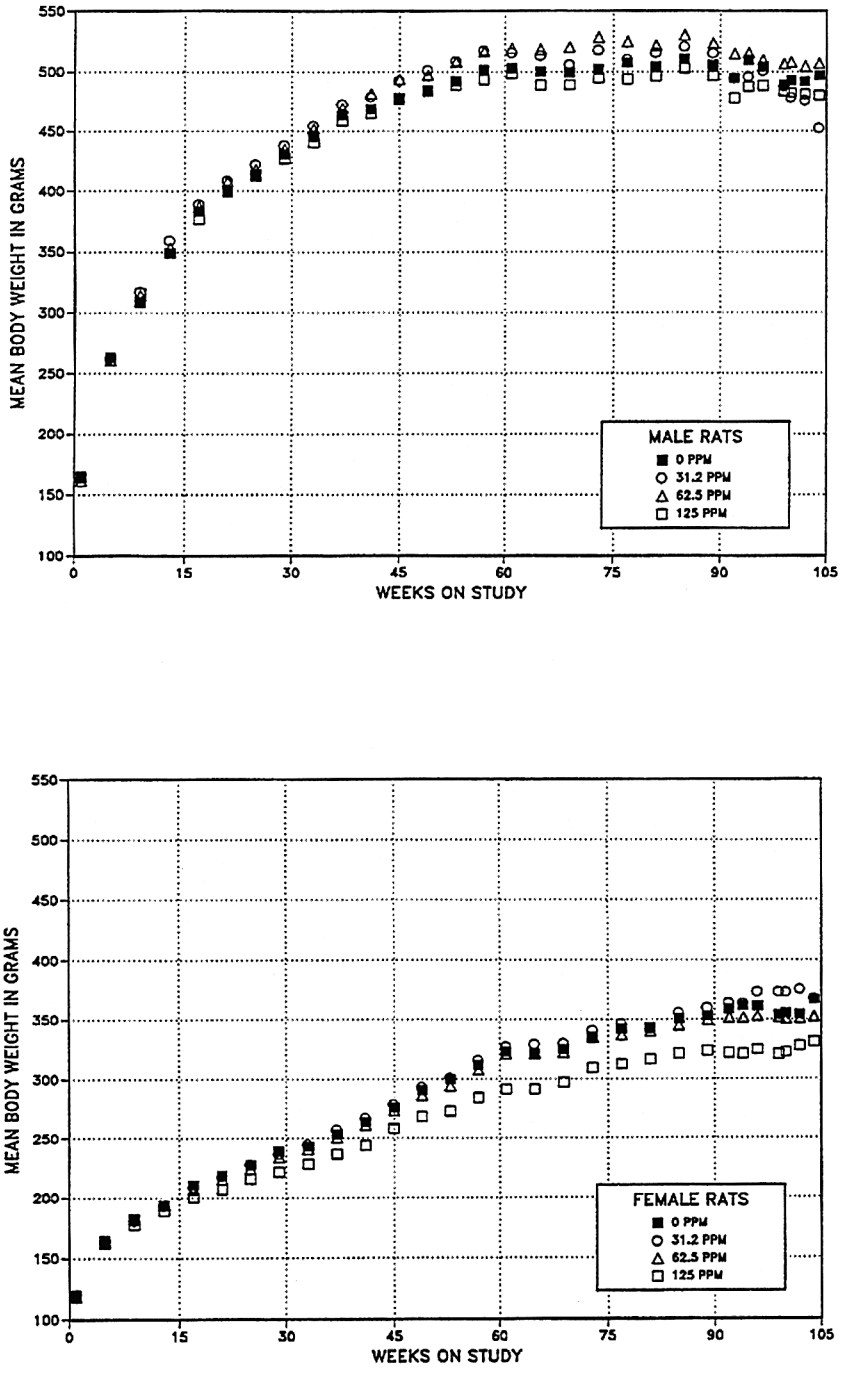

FIGURE 3
Growth Curves for Male and Female Rats
Exposed to 2-Butoxyethanol by Inhalation for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

Weeks on Study	Chamber Control		31.2 ppm			62.5 ppm			125 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	164	50	164	100	50	162	98	50	164	100	50
5	263	50	263	100	50	261	99	50	261	99	50
9	308	50	317	103	50	314	102	50	316	103	50
13	349	50	359	103	50	353	101	50	349	100	50
17	384	50	389	102	50	387	101	50	377	98	50
21	399	50	409	102	50	408	102	50	399	100	50
25	414	50	422	102	50	418	101	50	413	100	50
29	431	50	438	102	50	435	101	50	428	99	50
33	446	50	455	102	50	452	102	50	441	99	50
37	464	50	472	102	50	470	101	50	459	99	50
41	468	50	479	102	50	481	103	50	465	99	50
45	477	50	492	103	50	494	104	50	478	100	50
49	484	50	501	104	50	498	103	50	483	100	50
53	492	49	509	103	50	508	103	49	489	99	50
57	502	49	518	103	50	517	103	47	493	98	50
61	503	49	516	103	50	520	103	47	498	99	50
65	500	49	514	103	50	519	104	47	489	98	50
69	499	49	506	101	49	520	104	45	489	98	49
73	502	49	518	103	48	529	105	44	495	99	47
77	508	46	511	101	47	525	104	44	494	97	44
81	504	44	516	102	43	522	104	42	496	99	43
85	511	40	521	102	39	531	104	39	503	99	41
89	506	37	516	102	37	524	104	38	497	98	38
92	494	35	495	100	31	515	104	35	478	97	37
94	510	28	496	97	27	516	101	34	487	96	35
96	505	28	501	99	23	510	101	33	488	97	32
99	489	26	488	100	20	507	104	29	484	99	31
100	493	24	478	97	18	508	103	28	482	98	30
102	492	22	476	97	15	505	103	25	481	98	27
104	497	19	452	91	14	507	102	21	480	97	25
Mean for weeks											
1-13	271		276	102		273	101		273	101	
14-52	441		451	102		449	102		438	99	
53-104	500		502	100		517	103		490	98	

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

Weeks on Study	Chamber Control		31.2 ppm			62.5 ppm			125 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	120	50	119	99	50	118	99	50	119	99	50
5	164	50	164	100	50	163	100	50	162	99	50
9	182	50	181	99	50	182	100	50	177	97	50
13	194	50	193	100	50	194	100	50	189	98	50
17	210	50	209	99	50	207	98	50	201	95	50
21	218	50	218	100	50	216	99	50	207	95	50
25	227	50	228	101	50	224	99	50	216	95	50
29	239	50	237	99	50	234	98	50	222	93	50
33	243	50	245	101	50	241	99	50	228	94	50
37	253	50	257	102	50	250	99	49	237	94	50
41	264	50	267	101	50	261	99	49	244	93	50
45	276	50	278	101	50	273	99	49	258	94	50
49	290	50	293	101	50	286	99	49	268	92	50
53	300	50	301	101	50	294	98	49	273	91	50
57	312	50	316	101	50	308	99	48	284	91	50
61	323	49	327	101	50	322	100	48	291	90	50
65	321	49	329	102	50	322	100	48	291	91	50
69	325	49	330	102	50	322	99	46	297	92	48
73	335	49	341	102	49	335	100	45	309	92	48
77	342	48	346	101	49	337	99	44	313	91	48
81	343	45	342	100	47	340	99	42	317	92	46
85	350	44	356	102	44	345	99	39	321	92	45
89	353	43	360	102	42	350	99	38	324	92	42
92	359	41	364	102	41	352	98	36	322	90	40
94	362	39	363	101	40	352	97	34	321	89	38
96	361	37	373	103	37	353	98	33	325	90	34
99	354	37	373	106	35	352	100	32	321	91	31
100	355	35	373	105	33	351	99	29	323	91	28
102	354	35	376	106	31	351	99	26	328	93	22
104	367	30	368	100	30	353	96	25	331	90	22
Mean for weeks											
1-13	165		164	99		164	99		162	98	
14-52	247		248	100		244	99		231	94	
53-104	342		349	102		338	99		311	91	

Hematology and Bone Marrow Cellularity

The hematology data for rats are listed in Tables 9 and F2. As in the 14-week study, inhalation of 2-butoxyethanol by rats in the 2-year study resulted in the development of a persistent and exposure-related macrocytic, normochromic, responsive anemia. The anemia, evidenced by decreases in automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred at 3, 6, and 12 months in 62.5 ppm females and 125 ppm males and females. An anemia also occurred in 31.2 ppm females at 3 and 6 months, and there was evidence of an anemia in 62.5 ppm males at 12 months. Evidence of macrocytosis was demonstrated by increases in the mean cell volumes, accompanied by elevations in the mean cell hemoglobin values. The observed increases in reticulocyte and nucleated erythrocyte counts in males and/or females would be consistent with an erythropoietic response to the anemia. Increases in bone marrow cellularity occurred in 125 ppm females at all time points. Microscopic examination of the bone marrow preparations revealed approximate 15% to 35% decreases in the myeloid/erythroid (M/E) ratio for 125 ppm males and females during the study. Females exposed to 62.5 ppm generally had reduced M/E ratios of 10% to 30% during the study. Cytologically, morphologic alterations were observed and megakaryocytes were present in all exposed groups.

TABLE 9
Selected Hematology and Bone Marrow Cellularity Data for Rats at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Male				
Hematology				
n				
3 Months	9	9	9	9
6 Months	9	8	9	8
12 Months	8	0[b]	9	9
Automated hematocrit (mL/dL)				
3 Months	46.2 ± 0.3	48.5 ± 0.4	46.1 ± 0.4	43.5 ± 0.3**
6 Months	47.1 ± 0.3	46.5 ± 0.6	47.4 ± 0.7	44.3 ± 0.4**
12 Months	46.1 ± 0.3	—	44.4 ± 0.7**	41.4 ± 1.1**
Manual hematocrit (%)				
3 Months	44.9 ± 0.2	46.9 ± 0.5	44.8 ± 0.4	42.9 ± 0.5*
6 Months	47.2 ± 0.2	46.4 ± 0.5	47.2 ± 0.6	44.3 ± 0.7**
12 Months	47.8 ± 0.4	—	45.9 ± 0.8*	42.9 ± 1.2**
Hemoglobin (g/dL)				
3 Months	15.0 ± 0.1	15.5 ± 0.1	15.0 ± 0.1	14.2 ± 0.1**
6 Months	15.2 ± 0.1	15.1 ± 0.2	15.3 ± 0.2	14.4 ± 0.1**
12 Months	15.2 ± 0.0	—	14.7 ± 0.2**	13.4 ± 0.3**
Erythrocytes ($10^6/\mu L$)				
3 Months	8.99 ± 0.06	9.19 ± 0.06	8.84 ± 0.09	8.01 ± 0.06**
6 Months	9.02 ± 0.08	8.85 ± 0.10	9.05 ± 0.14	8.16 ± 0.07**
12 Months	8.88 ± 0.08	—	8.39 ± 0.15**	7.43 ± 0.20**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.12 ± 0.02	0.14 ± 0.01	0.14 ± 0.02	0.20 ± 0.01**
6 Months	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.14 ± 0.01**
12 Months	0.11 ± 0.03	—	0.13 ± 0.02	0.19 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)				
3 Months	0.01 ± 0.01	0.04 ± 0.03	0.02 ± 0.02	0.05 ± 0.02
6 Months	0.05 ± 0.02	0.00 ± 0.00*	0.01 ± 0.01	0.02 ± 0.01
12 Months	0.05 ± 0.02	—	0.15 ± 0.10	0.04 ± 0.03
Mean cell volume (fL)				
3 Months	51.3 ± 0.3	52.8 ± 0.1**	52.0 ± 0.2*	54.2 ± 0.3**
6 Months	52.3 ± 0.5	52.5 ± 0.2	52.4 ± 0.2	54.4 ± 0.2**
12 Months	52.0 ± 0.2	—	52.9 ± 0.3*	55.8 ± 0.2**
Mean cell hemoglobin (pg)				
3 Months	16.7 ± 0.1	16.9 ± 0.0	16.9 ± 0.1	17.7 ± 0.0**
6 Months	16.9 ± 0.1	17.1 ± 0.1*	16.9 ± 0.1	17.6 ± 0.1**
12 Months	17.1 ± 0.2	—	17.5 ± 0.1	18.1 ± 0.1**
Mean cell hemoglobin concentration (g/dL)				
3 Months	32.5 ± 0.1	32.0 ± 0.1*	32.4 ± 0.1	32.6 ± 0.1
6 Months	32.3 ± 0.3	32.5 ± 0.1	32.3 ± 0.1	32.4 ± 0.1
12 Months	33.0 ± 0.2	—	33.1 ± 0.2	32.5 ± 0.2

TABLE 9
Selected Hematology and Bone Marrow Cellularity Data for Rats at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Male (continued)				
Bone Marrow Cellularity				
n				
3 Months	9	0	9	9
6 Months	9	9	9	9
12 Months	9	0	9	9
Nucleated bone marrow cells (10^6/femur)				
3 Months	82.9 ± 3.1	—	82.5 ± 2.6	88.8 ± 3.7
6 Months	103.0 ± 3.0	102.8 ± 7.4	104.3 ± 4.7	110.6 ± 3.4
12 Months	111.5 ± 6.4	—	102.6 ± 3.3	128.1 ± 3.1
Myeloid/erythroid ratio				
3 Months	1.232 ± 0.056	—	1.063 ± 0.059	1.023 ± 0.062
6 Months	0.958 ± 0.042	1.122 ± 0.076	1.118 ± 0.101	0.826 ± 0.045
12 Months	1.107 ± 0.126	—	1.042 ± 0.058	0.720 ± 0.048**
Female				
Hematology				
n				
3 Months	8	9	9	9
6 Months	9	9	9	9
12 Months	9	0	8	9
Automated hematocrit (mL/dL)				
3 Months	48.9 ± 0.2	47.3 ± 0.5**	44.9 ± 0.5**	43.0 ± 0.4**
6 Months	46.0 ± 0.4	41.1 ± 1.5*	42.2 ± 0.9**	40.0 ± 0.3**
12 Months	44.2 ± 0.3	—	43.7 ± 0.3	40.7 ± 0.4**
Manual hematocrit (%)				
3 Months	46.5 ± 0.5	46.1 ± 0.5	43.3 ± 0.5**	42.2 ± 0.5**
6 Months	45.8 ± 0.4	41.9 ± 1.4*	43.1 ± 0.9**	41.4 ± 0.3**
12 Months	45.4 ± 0.2	—	45.3 ± 0.3	42.3 ± 0.4**
Hemoglobin (g/dL)				
3 Months	15.5 ± 0.1	14.8 ± 0.2**	14.3 ± 0.2**	13.7 ± 0.1**
6 Months	15.2 ± 0.1	13.7 ± 0.5**	13.9 ± 0.3**	13.2 ± 0.1**
12 Months	14.9 ± 0.1	—	14.6 ± 0.1	13.5 ± 0.1**
Erythrocytes ($10^6/\mu$L)				
3 Months	8.52 ± 0.03	8.10 ± 0.10**	7.54 ± 0.08**	7.08 ± 0.05**
6 Months	8.40 ± 0.07	7.50 ± 0.25**	7.54 ± 0.15**	6.89 ± 0.05**
12 Months	7.81 ± 0.05	—	7.42 ± 0.06**	6.75 ± 0.05**
Reticulocytes ($10^6/\mu$L)				
3 Months	0.13 ± 0.01	0.16 ± 0.02	0.18 ± 0.02	0.20 ± 0.02*
6 Months	0.06 ± 0.01	0.08 ± 0.01	0.12 ± 0.01**	0.17 ± 0.01**
12 Months	0.06 ± 0.01	—	0.11 ± 0.02*	0.12 ± 0.02**
Nucleated erythrocytes ($10^3/\mu$L)				
3 Months	0.10 ± 0.03	0.18 ± 0.02	0.09 ± 0.03	0.26 ± 0.05*
6 Months	0.05 ± 0.03	0.02 ± 0.02	0.03 ± 0.01	0.04 ± 0.02
12 Months	0.07 ± 0.02	—	0.05 ± 0.02	0.25 ± 0.08*
Mean cell volume (fL)				
3 Months	57.4 ± 0.2	58.3 ± 0.2**	59.6 ± 0.4**	60.7 ± 0.4**
6 Months	54.8 ± 0.3	54.8 ± 0.4	56.0 ± 0.3*	58.2 ± 0.2**
12 Months	56.8 ± 0.2	—	58.8 ± 0.3**	60.3 ± 0.3**

TABLE 9
Selected Hematology and Bone Marrow Cellularity Data for Rats at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Female (continued)				
Hematology (continued)				
n				
3 Months	8	9	9	9
6 Months	9	9	9	9
12 Months	9	0	8	9
Mean cell hemoglobin (pg)				
3 Months	18.2 ± 0.0	18.3 ± 0.1	18.9 ± 0.1**	19.3 ± 0.1**
6 Months	18.1 ± 0.1	18.3 ± 0.1	18.4 ± 0.1	19.2 ± 0.1**
12 Months	19.1 ± 0.1	—	19.7 ± 0.1**	20.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)				
3 Months	31.7 ± 0.1	31.3 ± 0.2	31.8 ± 0.2	31.8 ± 0.2
6 Months	33.2 ± 0.2	33.4 ± 0.2	32.9 ± 0.1	33.1 ± 0.1
12 Months	33.7 ± 0.2	—	33.6 ± 0.2	33.2 ± 0.2
Bone Marrow Cellularity				
n				
3 Months	8	0	9	9
6 Months	9	9	9	9
12 Months	9	0	8	9
Nucleated bone marrow cells (10^6/femur)				
3 Months	62.8 ± 4.4	—	68.4 ± 3.7	84.0 ± 2.0**
6 Months	63.6 ± 2.3	64.8 ± 4.8	64.0 ± 4.5	89.7 ± 2.4**
12 Months	74.3 ± 4.8	—	81.8 ± 4.4	110.1 ± 5.6**
Myeloid/erythroid ratio				
3 Months	1.060 ± 0.084	—	0.840 ± 0.036	0.744 ± 0.044**
6 Months	1.137 ± 0.061	1.037 ± 0.066	0.788 ± 0.040**	0.708 ± 0.025**
12 Months	0.846 ± 0.047	—	0.766 ± 0.031	0.690 ± 0.046*

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not examined at this exposure concentration

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the adrenal medulla, nose, liver, and spleen. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Adrenal Medulla: The incidences of benign or malignant pheochromocytoma (combined) occurred with a positive trend in females; however, the incidence in females exposed to 125 ppm was not significantly increased relative to the chamber controls (Tables 10 and B3) but exceeded the range for historical controls from 2-year inhalation studies (Tables 10 and B4).

One pheochromocytoma in the 125 ppm female group was malignant and another, while benign, was bilateral (Tables 10 and B1). The incidence of medullary hyperplasia was slightly, although not significantly, greater in females in the 125 ppm group than in the chamber controls (Tables 10 and B5).

The primary criterion used to distinguish pheochromocytoma from medullary hyperplasia was the presence of mild to moderate compression of the adjacent tissue. Most of the pheochromocytomas were small and not substantially larger than the more severe grades of adrenal medullary hyperplasia.

Nose: Incidences of hyaline degeneration of the olfactory epithelium were significantly increased in all exposed groups of males (chamber control, 13/48; 31.2 ppm, 21/49; 62.5 ppm, 23/49; 125 ppm, 40/50; Table A4) and in females exposed to 62.5 or 125 ppm (13/50, 18/48, 28/50, 40/49; Table B5); the severity of this lesion was not affected by exposure. This change has been shown to occur in control and exposed animals (Morgan and Harkema, 1996) and is considered to be the most common age-related change in the nasal passages of rats (St. Clair and Morgan, 1992). In exposure-related cases, this change has been proposed to have an adaptive/protective role (Buckley *et al.*, 1985). This lesion consisted of intracytoplasmic accumulation of homogeneous eosinophilic material, either unilaterally or involving both sides of the nose. The change was of minimal severity and was generally confined to the olfactory epithelium lining the dorsal meatus of level II, although in more severe cases it was also present in the olfactory epithelium of the ethmoid turbinates in level III. Two neoplasms in the nose were observed in this study: a chondroma in a 31.2 ppm male and an adenoma in a 62.5 ppm male (Table A1). Due to the sporadic occurrence of these neoplasms and the lack of any preneoplastic change in the nasal epithelium, they are considered to be incidental and likely not related to 2-butoxyethanol exposure.

Liver: The incidences of Kupffer cell pigmentation were significantly increased relative to the chamber controls in males (23/50, 30/50, 34/50, 42/50; Table A4) and females (15/50, 19/50, 36/50, 47/50; Table B5) exposed to 62.5 or 125 ppm; the severities of this lesion were increased in the 125 ppm groups (males: 1.3, 1.5, 1.5, 2.0; females: 1.4, 1.5, 1.4, 2.0).

Spleen: Incidences of splenic fibrosis were significantly increased relative to the chamber controls in males exposed to 62.5 or 125 ppm (11/50, 14/50, 19/50, 20/50; Table A4).

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Number Examined Microscopically	50	50	49	49
Hyperplasia[a]	11 (1.9)[b]	11 (2.3)	8 (2.1)	17 (2.5)
Benign Pheochromocytoma, Bilateral	0	0	0	1
Benign Pheochromocytoma (includes bilateral)[c]				
Overall rate[d]	3/50 (6%)	4/50 (8%)	1/49 (2%)	7/49 (14%)
Adjusted rate[e]	6.9%	9.2%	2.6%	16.7%
Terminal rate[f]	1/29 (3%)	1/27 (4%)	1/22 (5%)	1/21 (5%)
First incidence (days)	554	584	730 (T)	638
Poly-3 test[g]	P=0.090	P=0.499	P=0.353N	P=0.138
Malignant Pheochromocytoma	0	0	0	1
Benign or Malignant Pheochromocytoma[h]				
Overall rate	3/50 (6%)	4/50 (8%)	1/49 (2%)	8/49 (16%)
Adjusted rate	6.9%	9.2%	2.6%	18.9%
Terminal rate	1/29 (3%)	1/27 (4%)	1/22 (5%)	1/21 (5%)
First incidence (days)	554	584	730 (T)	612
Poly-3 test	P=0.044	P=0.499	P=0.353N	P=0.086

(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 47/889 (5.3% ± 3.9%); range, 0%-13%
[d] Number of animals with neoplasm per number of animals with adrenal gland examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[h] Historical incidence: 57/889 (6.4% ± 3.5%); range, 2%-13% (also includes complex and unspecified pheochromocytoma)

MICE

14-WEEK STUDY

Two male and two female mice exposed to 500 ppm died and two male and two female mice were killed moribund during the first 2 weeks of the study; all other mice survived until the end of the study (Table 11). The final mean body weights and body weight gains of 125, 250, and 500 ppm male mice were significantly less than those of the chamber controls. Clinical findings were observed only in males and females exposed to 500 ppm that died or were killed moribund and included abnormal breathing, red urine stains, and lethargy.

TABLE 11
Survival and Body Weights of Mice in the 14-Week Inhalation Study of 2-Butoxyethanol

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.6 ± 0.3	36.4 ± 0.8	11.8 ± 0.7	
31	10/10	24.6 ± 0.2	35.7 ± 0.6	11.1 ± 0.4	98
62.5	10/10	24.8 ± 0.3	36.2 ± 0.6	11.4 ± 0.5	99
125	10/10	24.7 ± 0.4	34.3 ± 0.7*	9.6 ± 0.5*	94
250	10/10	24.3 ± 0.3	34.2 ± 0.5*	10.0 ± 0.6*	94
500	6/10[c]	24.3 ± 0.2	32.0 ± 0.5**	7.7 ± 0.6**	88
Female					
0	10/10	19.3 ± 0.2	29.3 ± 0.6	10.0 ± 0.5	
31	10/10	19.6 ± 0.2	29.7 ± 0.8	10.1 ± 0.8	101
62.5	10/10	19.6 ± 0.2	30.2 ± 0.9	10.6 ± 0.8	103
125	10/10	19.5 ± 0.2	29.3 ± 0.6	9.8 ± 0.6	100
250	10/10	19.7 ± 0.2	30.2 ± 0.4	10.5 ± 0.5	103
500	6/10[c]	19.4 ± 0.4	28.3 ± 0.6	8.5 ± 0.6	97

* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 1, 1, 1, 2

The hematology data are listed in Tables 12 and F3. Similar to the rats, an exposure-concentration-related anemia, evidenced by decreases in automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in males exposed to 125 ppm or greater and in all exposed groups of females. Because the anemia occurred in all exposed female groups and was slightly more pronounced than in the males, females appeared to be more sensitive to 2-butoxyethanol. As in the rats, the anemia in mice was responsive, evidenced by increased reticulocyte counts; however, unlike the rats, the morphologic classification was normocytic and normochromic. Normocytic and normochromic erythrocytes were demonstrated by the lack of change in the mean cell volumes and mean cell hemoglobin concentrations, respectively. Platelet counts increased in 500 ppm males and females and 250 ppm females.

TABLE 12
Selected Hematology Data for Mice in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
n	10	10	10	10	10	6
Male						
Automated hematocrit (mL/dL)	47.7 ± 1.0	48.8 ± 0.4	48.0 ± 0.6	47.1 ± 0.5	44.2 ± 0.3**	35.1 ± 1.4**
Manual hematocrit (%)	47.3 ± 1.0	48.3 ± 0.4	47.6 ± 0.5	46.6 ± 0.4	44.2 ± 0.4**	36.3 ± 1.4**
Hemoglobin (g/dL)	15.7 ± 0.4	16.0 ± 0.1	15.9 ± 0.1	15.4 ± 0.1**	14.4 ± 0.1**	11.4 ± 0.4**
Erythrocytes ($10^6/\mu L$)	9.71 ± 0.22	10.04 ± 0.08	9.77 ± 0.10	9.47 ± 0.06*	8.90 ± 0.07**	7.21 ± 0.23**
Reticulocytes ($10^6/\mu L$)	0.21 ± 0.03	0.22 ± 0.03	0.21 ± 0.02	0.32 ± 0.03*	0.45 ± 0.04**	0.79 ± 0.20**
Mean cell volume (fL)	49.1 ± 0.4	48.5 ± 0.3	49.0 ± 0.4	49.7 ± 0.4	49.8 ± 0.4	48.3 ± 0.9
Mean cell hemoglobin (pg)	16.2 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	16.2 ± 0.0	16.2 ± 0.1	15.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.2	32.8 ± 0.3	33.0 ± 0.2	32.7 ± 0.2	32.5 ± 0.2	32.5 ± 0.3
Platelets ($10^3/\mu L$)	922.5 ± 29.9	878.0 ± 22.1	894.0 ± 23.7	933.5 ± 30.0	1,001.3 ± 46.4	1,176.7 ± 78.2*
Female						
Automated hematocrit (mL/dL)	47.1 ± 0.4	46.6 ± 0.3	46.4 ± 0.3	45.4 ± 0.5*	42.0 ± 0.4**	35.8 ± 0.7**
Manual hematocrit (%)	46.2 ± 0.3	45.9 ± 0.3	45.8 ± 0.3	45.1 ± 0.2**	42.3 ± 0.4**	37.8 ± 1.0**
Hemoglobin (g/dL)	15.7 ± 0.1	15.4 ± 0.1*	15.4 ± 0.1*	14.8 ± 0.1**	13.7 ± 0.1**	11.6 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.72 ± 0.05	9.55 ± 0.06*	9.51 ± 0.06*	9.18 ± 0.05**	8.57 ± 0.06**	7.35 ± 0.07**
Reticulocytes ($10^6/\mu L$)	0.18 ± 0.02	0.21 ± 0.03	0.19 ± 0.02	0.29 ± 0.02**	0.47 ± 0.04**	1.17 ± 0.28**
Mean cell volume (fL)	48.3 ± 0.3	48.8 ± 0.2	48.8 ± 0.2	49.5 ± 0.5	49.0 ± 0.3	48.8 ± 1.0
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	16.0 ± 0.0	15.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.2	33.0 ± 0.3	33.2 ± 0.2	32.6 ± 0.2	32.6 ± 0.2	32.4 ± 0.4*
Platelets ($10^3/\mu L$)	838.0 ± 19.0	779.7 ± 29.5	854.7 ± 18.1	930.3 ± 44.1	1,032.1 ± 44.1**	1,179.0 ± 75.6**

* Significantly different ($P \le 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

Microscopic evaluation of blood smears of mice in the 500 ppm groups revealed increased numbers of polychromatophilic erythrocytes.

Absolute and relative liver weights of 500 ppm males and relative liver weights of 250 ppm males and 500 ppm females were significantly greater than those of the chamber controls (Table G2). Male and female mice exposed to 500 ppm that either died or were killed moribund during the study exhibited a number of histopathologic changes (Table 13). Male mice had ulceration and necrosis of the forestomach. Female mice had full-wall-thickness forestomach necrosis, and one female had an ulcer in the glandular stomach. Acute inflammation surrounded the necrotic or ulcerative lesions. In addition to the focal inflammation, suppurative inflammation was present in the peritoneum of two males and on the mediastinal pleura of two males and two females. These lesions were considered to be secondary to gastric ulceration and/or necrosis with extension of the inflammation through the wall or perforation of the wall.

TABLE 13
Incidences of Selected Nonneoplastic Lesions in Mice that Died or Were Killed Moribund in the 14-Week Inhalation Study of 2-Butoxyethanol

	500 ppm			
	Male		Female	
Forestomach[a]	4		4	
Inflammation[b]	3	(2.0)[c]	3	(2.0)
Necrosis	2	(2.0)	3	(3.0)
Ulcer	2	(3.0)	0	
Epithelium, Hyperplasia	1	(1.0)	0	
Glandular Stomach	4		4	
Ulcer	0		1	(2.0)
Peritoneum	4		4	
Suppurative Inflammation	2	(2.0)	0	
Mediastinum	4		4	
Suppurative Inflammation	2	(2.0)	2	(2.0)
Spleen	4		4	
Atrophy	4	(2.3)	3	(3.0)
Thymus	4		4	
Atrophy	2	(3.5)	2	(3.0)
Lymph Nodes	4		4	
Atrophy	2	(2.0)	2	(2.5)
Liver	4		4	
Necrosis	0		1	(3.0)
Kidney	4		4	
Renal Tubule, Degeneration	4	(1.8)	3	(1.3)
Epididymis	4		—	
Necrosis	1	(1.0)	—	
Testis	4		—	
Degeneration	2	(2.0)	—	

[a] Number of animals that died or were killed moribund
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

In addition, lymphoid atrophy of the spleen, thymus, and mesenteric and mandibular lymph nodes occurred in males and females. Renal cortical degeneration and some necrosis were noted and were characterized by glandular eosinophilic debris in the lumen of the cortical tubules and pyknotic nuclei. There were also testicular degeneration and necrosis of the epididymis in male mice.

The types of lesions noted in mice at terminal sacrifice were similar between males and females (Table 14). Epithelial hyperplasia and inflammation of the muscularis or serosa of the forestomach occurred in females exposed to 125 ppm or greater. The minimal to mild forestomach inflammation consisted of focal infiltration of mixed mononuclear cells. Two male mice exposed to 500 ppm had

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Mice at Terminal Sacrifice in the 14-Week Inhalation Study of 2-Butoxyethanol

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Male						
Spleen[a]	10	10	10	10	10	6
Hematopoietic Cell Proliferation[b]	0	0	0	2 (1.0)[c]	9** (1.2)	6** (2.0)
Pigmentation, Hemosiderin	0	0	0	10** (1.0)	10** (1.0)	6** (1.0)
Liver	10	10	10	10	10	6
Kupffer Cell, Pigmentation, Hemosiderin	0	0	0	0	0	6** (1.0)
Forestomach	10	10	9	10	10	6
Epithelium, Hyperplasia	0	0	0	1 (1.0)	0	2 (1.0)
Kidney	10	10	10	10	10	6
Renal Tubule, Pigmentation, Hemosiderin	0	0	0	0	0	5** (1.0)
Female						
Spleen	10	10	10	10	10	6
Hematopoietic Cell Proliferation	0	0	0	0	1 (2.0)	6** (2.0)
Pigmentation, Hemosiderin	0	0	0	0	10** (1.0)	6** (1.0)
Liver	10	10	10	10	10	6
Kupffer Cell, Pigmentation, Hemosiderin	0	0	0	0	10** (1.0)	6** (1.0)
Forestomach	10	10	10	10	10	6
Inflammation	0	1 (1.0)	0	2 (1.0)	4* (1.0)	4** (1.3)
Epithelium, Hyperplasia	1 (1.0)	2 (1.5)	5 (1.2)	9** (1.8)	10** (1.7)	4** (2.0)
Kidney	10	10	10	10	10	6
Renal Tubule, Pigmentation, Hemosiderin	0	0	0	0	0	6** (1.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

epithelial hyperplasia of the forestomach, but the inflammatory process observed in females was not present. Extramedullary hematopoietic cell proliferation, primarily erythroid, and hemosiderin pigmentation of the spleen were present in males exposed to 125 ppm or greater and in females exposed to 250 or 500 ppm.

Hemosiderin pigmentation in Kupffer cells was the only change observed in the livers of males exposed to 500 ppm and females exposed to 250 or 500 ppm. The incidences of renal tubule hemosiderin pigmentation in males and females exposed to 500 ppm were significantly increased.

Exposure Concentration Selection Rationale: Mortality and significant hematologic effects observed at 500 ppm precluded the use of this concentration in the 2-year study; however, the hematologic effects in mice exposed to 250 ppm and the minimal inflammatory and hyperplastic lesions of the forestomach in female mice exposed to 250 ppm (although only

slightly less severe than those in 500 ppm females surviving to terminal sacrifice) were not considered sufficiently severe to preclude use of this concentration in a 2-year study. In addition, there were minimal exposure-related effects in male mice exposed to 125 or 250 ppm. Whenever possible in inhalation studies, males and females of a species for each concentration are housed in the same chamber for economic reasons. No space was available for mice in the rat chambers. Therefore, the 2-butoxyethanol concentrations selected for the 2-year inhalation study in mice were 62.5, 125, and 250 ppm.

2-YEAR STUDY

Survival

Survival of male mice exposed to 125 or 250 ppm was significantly less than that of the chamber control group; survival of all other exposed groups of mice was similar to the chamber controls (Table 15 and Figure 4).

Body Weights and Clinical Findings

The mean body weights of exposed male mice were generally less than those of the chamber control group during the last 6 months of the study (Figure 5 and Table 16). Mean body weights of exposed female mice were less than those of the chamber control group; the reductions were greater and occurred earlier than those observed in males (Figure 5 and Table 17). No clinical findings were attributed to 2-butoxyethanol exposure.

TABLE 15
Survival of Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	7	8	13	10
Natural deaths	4	3	10	14
Animals surviving to study termination	39	39	27	26
Percent probability of survival at end of study[a]	78	78	54	52
Mean survival (days)[b]	697	713	665	651
Survival analysis[c]	P=0.001	P=1.000N	P=0.021	P=0.015
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	1	0	0	0
Moribund	14	16	12	10
Natural deaths	6	3	5	4
Animals surviving to study termination	29	31	33	36
Percent probability of survival at end of study	60	62	66	72
Mean survival (days)	688	674	667	694
Survival analysis	P=0.254N	P=1.000N	P=0.741N	P=0.324N

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

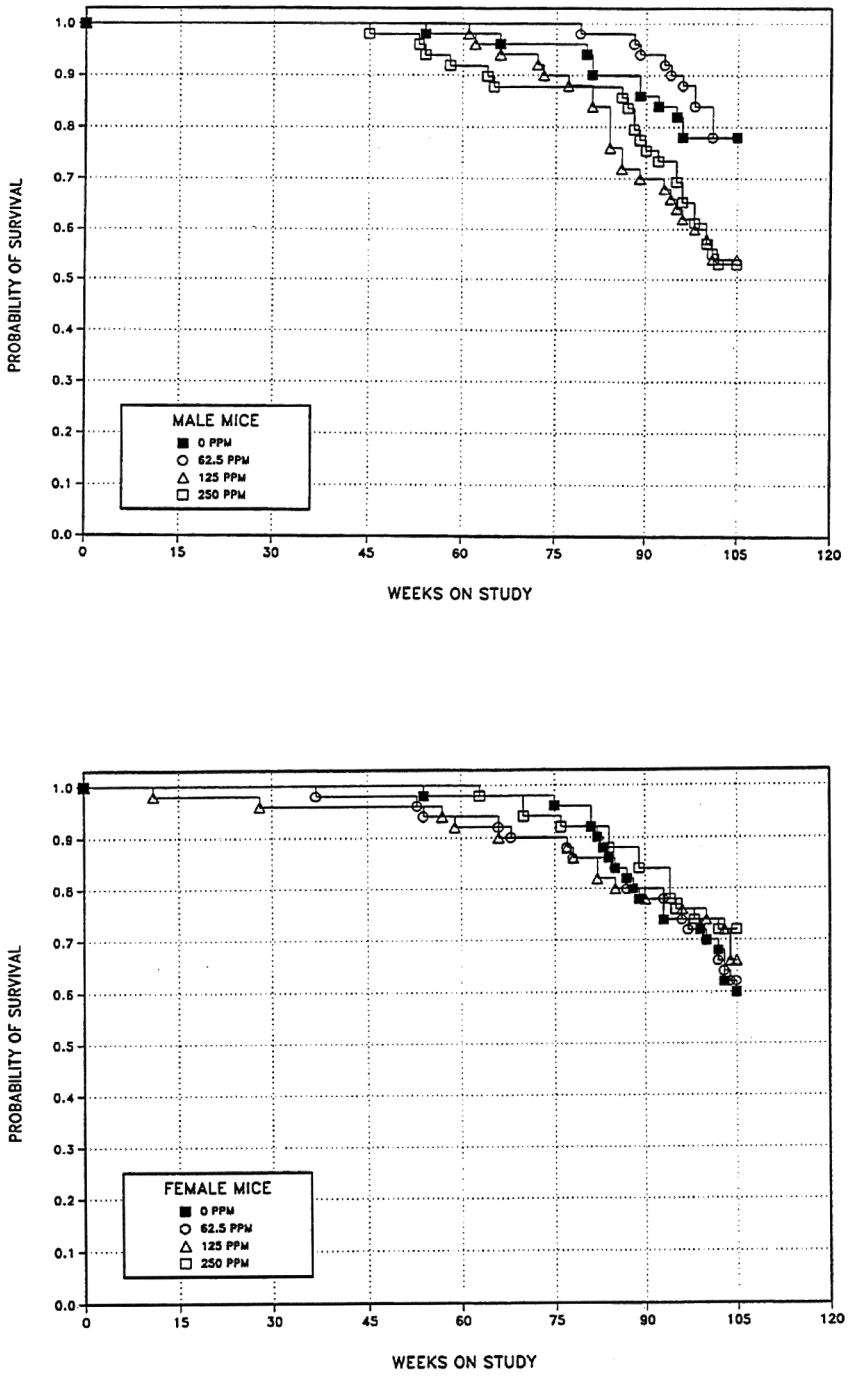

FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to 2-Butoxyethanol by Inhalation for 2 Years

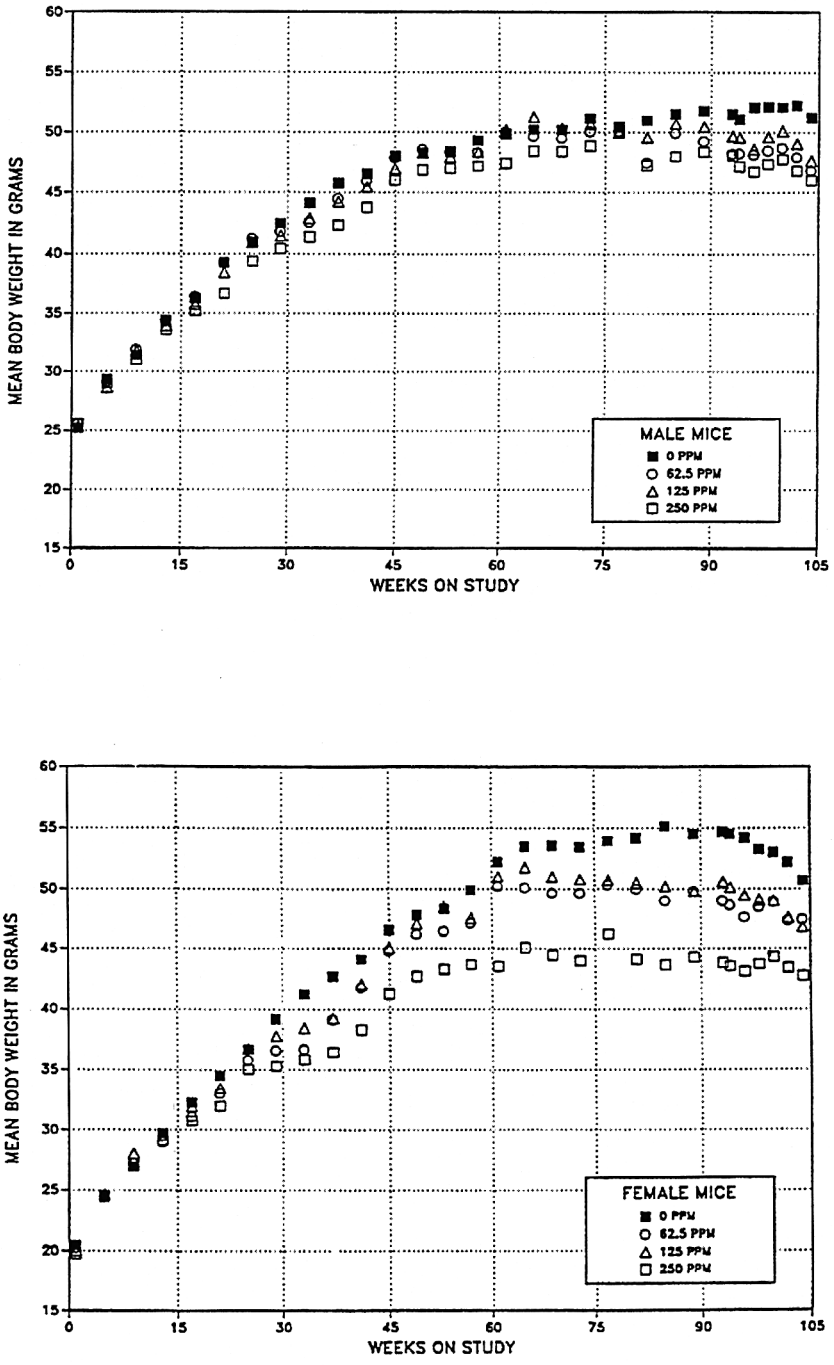

FIGURE 5
Growth Curves for Male and Female Mice
Exposed to 2-Butoxyethanol by Inhalation for 2 Years

TABLE 16
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

Weeks on Study	Chamber Control		62.5 ppm			125 ppm			250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	25.2	50	25.5	101	50	25.3	100	50	25.6	102	50
5	29.3	50	29.1	99	50	28.6	98	50	29.0	99	50
9	31.4	50	31.9	102	50	31.7	101	50	31.0	99	50
13	34.4	50	34.3	100	50	33.9	99	50	33.6	98	49
17	36.3	50	36.5	101	50	35.8	99	50	35.2	97	49
21	39.2	50	39.3	100	50	38.5	98	50	36.7	94	49
25	41.0	50	41.2	101	50	40.9	100	50	39.4	96	49
29	42.4	50	41.8	99	50	41.5	98	50	40.4	95	49
33	44.1	50	42.5	96	50	42.9	97	50	41.4	94	49
37	45.8	50	44.5	97	50	44.3	97	50	42.3	92	49
41	46.6	50	46.0	99	50	45.5	98	50	43.8	94	49
45	48.0	50	47.9	100	50	47.0	98	50	46.1	96	48
49	48.3	50	48.6	101	50	48.3	100	50	46.9	97	48
53	48.4	50	48.4	100	50	48.0	99	50	47.0	97	47
57	49.3	49	48.3	98	50	48.4	98	50	47.2	96	46
61	49.9	49	50.0	100	50	50.2	101	49	47.5	95	45
65	50.2	49	49.7	99	50	51.3	102	48	48.5	97	44
69	50.2	48	49.5	99	50	50.3	100	47	48.4	96	43
73	51.1	48	50.1	98	50	50.7	99	46	48.9	96	43
77	50.5	48	50.1	99	50	50.0	99	45	50.1	99	43
81	51.0	46	47.5	93	49	49.6	97	43	47.3	93	43
85	51.5	45	49.9	97	49	50.7	98	38	48.0	93	43
89	51.8	44	49.3	95	48	50.5	98	35	48.4	93	39
93	51.5	42	48.2	94	47	49.7	97	34	48.1	93	36
94	51.1	42	48.3	95	46	49.6	97	33	47.2	92	36
96	52.0	39	48.2	93	45	48.6	94	32	46.8	90	34
98	52.1	39	48.5	93	42	49.6	95	30	47.4	91	32
100	52.1	39	48.7	94	42	50.1	96	29	47.8	92	28
102	52.2	39	48.0	92	39	49.1	94	27	46.9	90	26
104	51.2	39	46.8	91	39	47.7	93	27	46.1	90	26
Mean for weeks											
1-13	30.1		30.2	100		29.9	99		29.8	99	
14-52	43.5		43.1	99		42.7	98		41.4	95	
53-104	50.9		48.8	96		49.7	98		47.7	94	

TABLE 17
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

Weeks on Study	Chamber Control Av. Wt. (g)	Chamber Control No. of Survivors	62.5 ppm Av. Wt. (g)	62.5 ppm Wt. (% of controls)	62.5 ppm No. of Survivors	125 ppm Av. Wt. (g)	125 ppm Wt. (% of controls)	125 ppm No. of Survivors	250 ppm Av. Wt. (g)	250 ppm Wt. (% of controls)	250 ppm No. of Survivors
1	20.4	50	20.3	100	50	20.1	99	50	19.8	97	50
5	24.4	50	24.5	100	50	24.6	101	50	24.5	100	50
9	27.0	50	27.2	101	50	28.0	104	50	27.2	101	50
13	29.7	50	29.0	98	50	29.6	100	49	29.1	98	50
17	32.3	50	31.1	96	50	32.0	99	49	30.8	95	50
21	34.5	50	33.0	96	50	33.5	97	49	32.0	93	50
25	36.7	50	35.8	98	50	36.8	100	49	35.0	95	50
29	39.2	50	36.6	93	50	37.8	96	48	35.3	90	50
33	41.2	50	36.7	89	50	38.4	93	48	35.9	87	50
37	42.7	50	39.2	92	49	39.3	92	48	36.5	86	50
41	44.1	50	41.8	95	49	42.1	96	48	38.3	87	50
45	46.6	50	44.8	96	49	45.1	97	48	41.3	89	50
49	47.8	50	46.2	97	49	47.1	99	48	42.7	89	50
53	48.3	50	46.5	96	49	48.5	100	48	43.3	90	50
57	49.9	49	47.2	95	47	47.6	95	48	43.7	88	50
61	52.2	49	50.2	96	47	51.1	98	46	43.6	84	50
65	53.5	49	50.1	94	47	51.8	97	46	45.1	84	49
69	53.6	49	49.6	93	45	51.0	95	45	44.5	83	49
73	53.5	49	49.6	93	45	50.8	95	45	44.0	82	47
77	53.9	48	50.4	94	44	50.8	94	44	46.2	86	46
81	54.2	47	50.0	92	43	50.5	93	43	44.2	82	46
85	55.1	42	49.0	89	43	50.2	91	41	43.7	79	44
89	54.5	40	49.8	91	40	49.8	91	40	44.3	81	43
93	54.7	38	49.0	90	39	50.6	93	39	43.8	80	42
94	54.5	37	48.6	89	39	50.1	92	39	43.6	80	41
96	54.2	37	47.6	88	39	49.4	91	38	43.1	80	38
98	53.3	37	48.5	91	36	49.1	92	38	43.7	82	37
100	53.0	36	48.9	92	35	49.0	93	38	44.4	84	37
102	52.2	35	47.4	91	35	47.6	91	37	43.4	83	36
104	50.7	30	47.5	94	31	46.8	92	33	42.8	84	36
Mean for weeks											
1-13	25.4		25.3	100		25.6	101		25.2	99	
14-52	40.6		38.4	95		39.1	96		36.4	90	
53-104	53.0		48.8	92		49.7	94		44.0	83	

Hematology and Bone Marrow Cellularity

The hematology data are listed in Tables 18 and F4. As in the 14-week study, inhalation of 2-butoxyethanol by mice in the 2-year study resulted in the development of a persistent, exposure-related, responsive anemia. The anemia, evidenced by decreases in automated and manual hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred at 3, 6, and 12 months in 125 and 250 ppm male and female mice; there also was evidence indicating an anemia at 6 months in 62.5 ppm females. The erythropoietic response was demonstrated by increased reticulocyte counts in 125 and 250 ppm male and female mice at 3 and 6 months and 250 ppm females at 12 months. The reticulocyte response ameliorated for 125 and 250 ppm males and 125 ppm females at 12 months. In general, the anemia was normocytic and normochromic and was demonstrated by the lack of changes in the mean cell volumes and mean cell hemoglobin concentrations. At 12 months, however, a minimal increase in the mean cell volume, suggesting a macrocytosis, occurred in 250 ppm females. A thrombocytosis, evidenced by increased platelet counts, occurred in 250 ppm males and females at 3, 6, and 12 months. Platelet counts also were increased in 125 ppm females at 6 months and 62.5 ppm females and 125 males and females at 12 months. Increased neutrophil counts occurred in 125 ppm males and females at 6 months and 125 and 250 ppm females at 12 months. Unlike the rats, there were no increases in the total bone marrow cell counts or decreases in the M/E ratios of exposed mice at any time point.

TABLE 18
Selected Hematology and Bone Marrow Cellularity Data for Mice at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Hematology				
n				
3 Months	10	10	10	10
6 Months	10	10	10	10
12 Months	10	10	9	10
Automated hematocrit (mL/dL)				
3 Months	46.3 ± 0.4	46.3 ± 0.3	44.9 ± 0.5*	42.5 ± 0.2**
6 Months	48.1 ± 0.4	47.6 ± 0.5	46.6 ± 0.3*	43.4 ± 0.4**
12 Months	48.8 ± 0.5	50.1 ± 2.0	47.0 ± 1.0	42.4 ± 0.5**
Manual hematocrit (%)				
3 Months	47.5 ± 0.3	47.3 ± 0.5	46.0 ± 0.4*	43.7 ± 0.2**
6 Months	48.1 ± 0.4	48.1 ± 0.4	47.2 ± 0.4	44.5 ± 0.3**
12 Months	47.9 ± 0.4	48.7 ± 1.9	46.4 ± 1.0	42.1 ± 0.4**
Hemoglobin (g/dL)				
3 Months	15.2 ± 0.1	15.3 ± 0.1	14.7 ± 0.2	13.8 ± 0.1**
6 Months	15.7 ± 0.2	15.6 ± 0.1	15.2 ± 0.1**	14.3 ± 0.1**
12 Months	15.7 ± 0.1	16.0 ± 0.7	14.9 ± 0.4*	13.6 ± 0.2**
Erythrocytes ($10^6/\mu L$)				
3 Months	9.61 ± 0.22	9.83 ± 0.06	9.41 ± 0.11	8.95 ± 0.05**
6 Months	9.88 ± 0.10	9.79 ± 0.08	9.58 ± 0.07*	9.09 ± 0.07**
12 Months	9.58 ± 0.07	9.73 ± 0.49	9.36 ± 0.32*	8.33 ± 0.10**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.13 ± 0.01**
6 Months	0.05 ± 0.01	0.07 ± 0.01	0.09 ± 0.01**	0.17 ± 0.01**
12 Months	0.06 ± 0.02	0.06 ± 0.02	0.11 ± 0.02	0.07 ± 0.02
Mean cell volume (fL)				
3 Months	48.6 ± 1.2	47.1 ± 0.2	47.7 ± 0.2	47.4 ± 0.3
6 Months	48.8 ± 0.4	48.6 ± 0.3	48.6 ± 0.3	47.8 ± 0.2
12 Months	50.9 ± 0.3	51.7 ± 0.5	50.3 ± 0.8	51.1 ± 0.6
Mean cell hemoglobin (pg)				
3 Months	15.9 ± 0.4	15.5 ± 0.0	15.7 ± 0.0	15.4 ± 0.1
6 Months	15.9 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	15.7 ± 0.1
12 Months	16.4 ± 0.1	16.5 ± 0.2	16.0 ± 0.3	16.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)				
3 Months	32.8 ± 0.1	33.0 ± 0.1	32.8 ± 0.1	32.4 ± 0.1
6 Months	32.6 ± 0.2	32.9 ± 0.2	32.7 ± 0.2	32.9 ± 0.2
12 Months	32.2 ± 0.2	32.0 ± 0.1	31.7 ± 0.3	31.9 ± 0.1
Platelets ($10^3/\mu L$)				
3 Months	904.2 ± 18.3	888.2 ± 11.7	869.8 ± 13.4	940.6 ± 18.9
6 Months	988.3 ± 16.8	955.4 ± 34.1	1,028.8 ± 20.6	1,075.2 ± 17.1**
12 Months	831.2 ± 38.1	997.6 ± 37.8**	1,116.6 ± 69.5**	1,112.8 ± 39.4**
Segmented neutrophils ($10^3/\mu L$)				
3 Months	0.67 ± 0.11	0.73 ± 0.08	0.81 ± 0.09	0.95 ± 0.15
6 Months	0.43 ± 0.08	0.43 ± 0.04	0.75 ± 0.09*	0.62 ± 0.09
12 Months	0.80 ± 0.04	0.84 ± 0.12	0.80 ± 0.13	0.70 ± 0.08

TABLE 18
Selected Hematology and Bone Marrow Cellularity Data for Mice at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male (continued)				
Bone Marrow Cellularity				
n				
3 Months	10	10	10	10
6 Months	10	10	10	10
12 Months	10	10	9	10
Nucleated bone marrow cells (10^6/femur)				
3 Months	23.4 ± 0.8	22.8 ± 0.6	22.1 ± 1.1	23.5 ± 0.9
6 Months	23.8 ± 0.9	23.3 ± 1.0	23.5 ± 1.2	24.3 ± 1.4
12 Months	32.9 ± 0.9	28.9 ± 0.9	30.1 ± 1.3	30.0 ± 1.5
Myeloid/erythroid ratio				
3 Months	1.99 ± 0.10	2.11 ± 0.10	1.98 ± 0.13	2.02 ± 0.06
6 Months	1.88 ± 0.08[b]	2.24 ± 0.10	2.33 ± 0.09**	2.10 ± 0.09
12 Months	1.78 ± 0.12	2.15 ± 0.07	2.34 ± 0.07**	2.06 ± 0.10
Female				
Hematology				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	10	10
Automated hematocrit (mL/dL)				
3 Months	48.9 ± 0.5	48.2 ± 0.3	46.0 ± 0.4**	42.8 ± 0.4**
6 Months	48.2 ± 0.5	46.2 ± 0.6*	45.7 ± 0.3**	42.5 ± 0.3**
12 Months	47.4 ± 0.5	46.9 ± 0.5	43.7 ± 0.6**	42.4 ± 0.4**
Manual hematocrit (%)				
3 Months	49.3 ± 0.5	48.9 ± 0.4	46.2 ± 0.5**	43.7 ± 0.5**
6 Months	48.1 ± 0.6	46.6 ± 0.5*	45.7 ± 0.2**	42.8 ± 0.2**
12 Months	46.9 ± 0.4	46.3 ± 0.4	43.8 ± 0.4**	41.8 ± 0.3**
Hemoglobin (g/dL)				
3 Months	15.5 ± 0.2	15.3 ± 0.1	14.6 ± 0.1**	13.4 ± 0.3**
6 Months	15.6 ± 0.2	14.9 ± 0.2**	14.7 ± 0.1**	13.6 ± 0.1**
12 Months	15.4 ± 0.1	15.0 ± 0.1*	14.3 ± 0.1**	13.6 ± 0.1**
Erythrocytes ($10^6/\mu$L)				
3 Months	9.89 ± 0.09	9.68 ± 0.07	9.23 ± 0.09**	8.58 ± 0.07**
6 Months	9.71 ± 0.15	9.33 ± 0.12*	9.19 ± 0.06**	8.68 ± 0.05**
12 Months	9.32 ± 0.09	9.14 ± 0.08	8.50 ± 0.12**	8.08 ± 0.09**
Reticulocytes ($10^6/\mu$L)				
3 Months	0.05 ± 0.00	0.06 ± 0.01	0.09 ± 0.01**	0.16 ± 0.01**
6 Months	0.05 ± 0.01	0.06 ± 0.01	0.09 ± 0.01**	0.14 ± 0.01**
12 Months	0.10 ± 0.01	0.14 ± 0.02	0.15 ± 0.02	0.24 ± 0.03**
Mean cell volume (fL)				
3 Months	49.3 ± 0.3	49.7 ± 0.2	49.8 ± 0.3	49.8 ± 0.1
6 Months	49.8 ± 0.6	49.5 ± 0.3	49.8 ± 0.4	49.0 ± 0.3
12 Months	50.9 ± 0.3	51.3 ± 0.3	51.5 ± 0.2	52.4 ± 0.3**

TABLE 18
Selected Hematology and Bone Marrow Cellularity Data for Mice at 3, 6, and 12 Months in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Female (continued)				
Hematology (continued)				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	10	10
Mean cell hemoglobin (pg)				
3 Months	15.7 ± 0.1	15.8 ± 0.0	15.8 ± 0.1	15.7 ± 0.1
6 Months	16.1 ± 0.2	16.0 ± 0.1	16.0 ± 0.1	15.7 ± 0.1
12 Months	16.6 ± 0.1	16.5 ± 0.1	16.8 ± 0.1	16.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)				
3 Months	31.8 ± 0.1	31.7 ± 0.1	31.7 ± 0.1	31.4 ± 0.1*
6 Months	32.4 ± 0.2	32.3 ± 0.2	32.1 ± 0.1	32.1 ± 0.1
12 Months	32.6 ± 0.2	32.2 ± 0.2	32.7 ± 0.2	32.0 ± 0.2
Platelets ($10^3/\mu L$)				
3 Months	835.8 ± 27.5	832.9 ± 26.9	849.9 ± 12.4	921.3 ± 23.3*
6 Months	938.6 ± 27.2	942.5 ± 34.9	1,010.6 ± 24.9*	1,064.6 ± 12.9**
12 Months	778.1 ± 28.2	837.6 ± 14.0*	844.5 ± 28.6**	952.9 ± 12.1**
Segmented neutrophils ($10^3/\mu L$)				
3 Months	0.49 ± 0.11	0.38 ± 0.05	0.50 ± 0.07	0.59 ± 0.05
6 Months	0.50 ± 0.05	0.83 ± 0.25	1.05 ± 0.31*	0.74 ± 0.07
12 Months	0.56 ± 0.06	0.79 ± 0.14	0.75 ± 0.06*	0.88 ± 0.09**
Bone Marrow Cellularity				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	9	10
Nucleated bone marrow cells (10^6/femur)				
3 Months	23.0 ± 0.9	22.7 ± 1.0	23.2 ± 0.7	22.9 ± 0.9
6 Months	26.5 ± 0.9	26.3 ± 1.6	24.6 ± 1.2	26.9 ± 0.5
12 Months	32.7 ± 1.0	31.0 ± 1.9	34.7 ± 1.0	35.8 ± 1.0
Myeloid/erythroid ratio				
3 Months	1.72 ± 0.12	2.03 ± 0.10	2.19 ± 0.10*	1.52 ± 0.09[c]
6 Months	1.81 ± 0.06	1.94 ± 0.13	2.08 ± 0.07*	1.90 ± 0.07
12 Months	1.53 ± 0.10	1.98 ± 0.08*	1.94 ± 0.13	1.59 ± 0.11

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=10

Pathology and Statistical Analysis

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

Forestomach: The incidences of squamous cell papilloma and squamous cell papilloma or carcinoma (combined) occurred with a positive trend in females, and the incidences in females exposed to 250 ppm were significantly increased relative to the chamber controls (Tables 19 and D3). These incidences exceeded the ranges for historical controls (Tables 19 and D4a). In male mice exposed to 125 or 250 ppm, the incidences of squamous cell papilloma also exceeded the range for historical controls (Tables 19 and C4a). A squamous cell carcinoma was observed in a male mouse exposed to 125 ppm; this mouse also had a papilloma. Squamous cell papilloma had the morphology typical of these neoplasms in B6C3F$_1$ mice and consisted of multiple branching papillary projections, composed of a thick layer of epithelium overlying a fibrous tissue core, radiating from a basal stalk (Plate 5). The squamous cell carcinoma was characterized by the invasion of cords or clusters of neoplastic cells through the forestomach wall (Plates 6 and 7). Incidences of ulcer were significantly increased relative to the chamber controls in males exposed to 125 ppm and in all exposed groups of females (Tables 19, C5, and D5). Ulcer consisted of a defect in the forestomach wall that penetrated the full thickness of the forestomach epithelium. The ulcerated area frequently contained accumulations of inflammatory cells and debris. Incidences of epithelial hyperplasia, usually focal, were significantly increased in all exposed groups of males and females. Frequently, particularly in the females, the hyperplasia was associated with ulceration. Hyperplasia consisted of an increased thickness of the stratified squamous epithelium of the forestomach; this was accompanied in some cases by an increase in the thickness of the keratinized layer (Plate 8).

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Forestomach in Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Number Necropsied	50	50	50	50
Ulcer[a]	1 (1.0)[b]	2 (1.5)	9** (1.6)	3 (1.7)
Epithelium, Hyperplasia	1 (3.0)	7* (2.3)	16** (1.8)	21** (2.3)
Number Examined Microscopically	50	50	49	48
Squamous Cell Papilloma	1	1	2	2
Squamous Cell Carcinoma	0	0	1	0
Squamous Cell Papilloma or Carcinoma[c]	1	1	2	2
Female				
Number Necropsied	50	50	50	50
Ulcer	1 (3.0)	7* (1.3)	13** (1.5)	22** (1.4)
Epithelium, Hyperplasia	6 (1.8)	27** (2.0)	42** (2.4)	44** (2.9)
Squamous Cell Papilloma[d]				
Overall rate[e]	0/50 (0%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate[f]	0.0%	2.4%	4.8%	11.2%
Terminal rate[g]	0/29 (0%)	1/31 (3%)	2/33 (6%)	3/36 (8%)
First incidence (days)	—[i]	731 (T)	731 (T)	582
Poly-3 test[h]	P=0.008	P=0.495	P=0.231	P=0.034
Squamous Cell Carcinoma	0	0	0	1
Squamous Cell Papilloma or Carcinoma[j]				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	2.4%	4.8%	13.4%
Terminal rate	0/29 (0%)	1/31 (3%)	2/33 (6%)	4/36 (11%)
First incidence (days)	—	731 (T)	731 (T)	582
Poly-3 test	P=0.002	P=0.495	P=0.231	P=0.017

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 5/970 (0.5% ± 0.9%); range, 0%-2%
[d] Historical incidence: 7/973 (0.7% ± 1.0%); range, 0%-2%
[e] Number of animals with neoplasm per number of animals with forestomach examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 9/973 (0.9% ± 1.1%); range, 0%-3%

Liver: The incidences of hemangiosarcoma occurred with a positive trend in male mice. The incidence of hemangiosarcoma in males exposed to 250 ppm was significantly increased relative to the chamber controls and exceeded the range of historical controls (Tables 20 and C3). Hemangiosarcomas had a morphological structure similar to that of spontaneously occurring hemangiosarcomas, such as the presence of atypical endothelial cells that form capillary and cavernous channels and the presence of solid cellular masses and local invasion. Two of the four 250 ppm mice with hemangiosarcomas also had hemangiosarcomas in either the bone marrow and heart or bone marrow and spleen. Due to the extreme infiltration in the bone marrow and spleen, it was not possible to determine whether these were the primary or metastatic foci for the hemangiosarcomas. The incidences of hepatocellular carcinoma occurred with a positive trend in male mice. The incidence of hepatocellular carcinoma in males exposed to 250 ppm was significantly increased relative to the chamber controls.

In assessing potential chemical-related increases in the incidences of liver neoplasms, benign and malignant neoplasms are routinely analyzed independently and in combination. Although the independent analyses provide useful information, the most important analysis for determining potential chemical-related effects in the liver is the combined analysis (hepatocellular adenoma and carcinoma). There was no difference in the combined incidence of hepatocellular neoplasms between chamber control and exposed groups (Tables 20, C3, and C4). While the statistically significant increased incidence of hepatocellular carcinoma in 250 ppm males may suggest a progression toward malignancy, the incidence of hepatocellular carcinoma in this group is well within the historical control range. Additionally, there were significant decreases in the incidences of hepatocellular adenoma in 125 and 250 ppm female mice, while the combined hepatocellular neoplasm incidences were not different between groups. Also, there was no increase in the incidence of potential preneoplastic lesions (e.g., altered foci). The decreased incidences of hepatocellular adenoma in 125 and 250 ppm females were interpreted as normal variations based upon chance rather than effects associated with exposure to 2-butoxyethanol. The increased incidence of hepatocellular carcinoma in 250 ppm males may have been caused by exposure to 2-butoxyethanol.

In a retrospective evaluation, a bacterial organism, *Helicobacter hepaticus*, has been identified in the livers of mice from several 2-year carcinogenicity studies conducted by the NTP (Hailey *et al.*, 1998). In the studies in which significant liver disease was attributable to *H. hepaticus*, an association with increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma of the liver) was demonstrated. The most definitive method of identifying the presence of *H. hepaticus* is with polymerase chain reaction-based assays on fresh or frozen liver tissue. However, in other studies in which liver disease was associated with the presence of the organism, the use of silver stains (e.g., Steiner's modification of Warthin-Starry) has also been effective in identifying a helical organism consistent with *H. hepaticus*. Fresh or frozen liver tissue was not available from this study; therefore, sections of liver from six males from the chamber control group and eight from the 250 ppm group were stained with Steiner's modification of the Warthin-Starry silver stain and evaluated for *H. hepaticus*. While inflammation, karyomegaly, and oval cell hyperplasia are nonspecific liver lesions that can be observed under a number of circumstances, they are consistent components of the liver disease observed in male mice infected with *H. hepaticus*. Therefore, to maximize the potential for identifying *H. hepaticus* in this study, the 14 animals were selected for staining based on the presence of these lesions in the liver. No organisms consistent with *H. hepaticus* were identified in any of the 14 animals evaluated; therefore, *H. hepaticus* was not considered to have been a factor in the development of liver neoplasms in this study.

Incidences of hemosiderin pigmentation in the Kupffer cells were significantly increased in males exposed to 125 or 250 ppm and in all exposed groups of females (Tables 20, C5, and D5).

TABLE 20
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Number Examined Microscopically	50	50	49	49
Kupffer Cell, Pigmentation, Hemosiderin[a]	0	0	8** (1.0)[b]	30** (1.2)
Hemangiosarcoma[c]				
Overall rate[d]	0/50 (0%)	1/50 (2%)	2/49 (4%)	4/49 (8%)
Adjusted rate[e]	0.0%	2.1%	5.0%	10.0%
Terminal rate[f]	0/39 (0%)	0/39 (0%)	1/27 (4%)	2/26 (8%)
First incidence (days)	—[h]	670	704	454
Poly-3 test[g]	P=0.014	P=0.511	P=0.211	P=0.046
Hepatocellular Adenoma	22	18	18	17
Hepatocellular Carcinoma[i]	10	11	16	21**
Hepatocellular Adenoma or Carcinoma[j]	30	24	31	30
Female				
Number Examined Microscopically	50	50	49	50
Kupffer Cell, Pigmentation, Hemosiderin	0	5* (1.0)	25** (1.0)	44** (1.0)
Hemangiosarcoma	0	1	0	0
Hepatocellular Adenoma[k]	16	8	7*	8*
Hepatocellular Carcinoma	10	12	13	10
Hepatocellular Adenoma or Carcinoma	22	16	18	18

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 14/968 (1.5% ± 1.5%); range, 0%-4%
[d] Number of animals with neoplasm per number of animals microscopically examined
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 247/968 (25.7% ± 10.4%); range, 11%-48%
[j] Historical incidence: 503/968 (52.2% ± 16.4%); range, 20%-86%
[k] Historical incidence: 191/968 (19.8% ± 10.2%); range, 8%-43%

Spleen: Incidences of hematopoietic cell proliferation in males exposed to 125 or 250 ppm and females exposed to 250 ppm were significantly increased relative to the chamber controls (Tables 21, C5, and D5). This lesion consisted of excess production of cells with no apparent change in M/E ratios. Incidences of hemosiderin pigmentation were significantly increased in all exposed groups of males and in females exposed to 125 or 250 ppm. Hematopoietic cell proliferation and hemosiderin pigmentation were attributed to the primary hemolytic effect of 2-butoxyethanol, which was followed by regenerative hyperplasia of the hematopoietic tissue.

TABLE 21
Incidences of Nonneoplastic Lesions of the Spleen in Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Number Examined Microscopically	50	50	48	49
Hematopoietic Cell Proliferation[a]	12 (1.8)[b]	11 (2.5)	26** (2.3)	42** (2.4)
Hemosiderin Pigmentation	0	6* (1.0)	45** (1.6)	44** (1.9)
Female				
Number Examined Microscopically	50	50	49	50
Hematopoietic Cell Proliferation	24 (2.5)	29 (2.4)	32 (2.2)	35* (2.1)
Hemosiderin Pigmentation	39 (1.5)	44 (1.8)	46** (1.9)	48** (2.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Bone Marrow: Incidences of hyperplasia in males exposed to 125 or 250 ppm were significantly increased relative to the chamber controls (0/50, 1/50, 9/49, 5/50; Table C5).

Nose: The incidences of hyaline degeneration were increased relative to the chamber controls in the olfactory epithelium (6/50, 14/50, 11/49, 12/50) and in the respiratory epithelium (17/50, 35/50, 26/49, 23/50) of exposed groups of females (Table D5); however, the severities of these lesions were similar to those in the chamber controls (olfactory: 1.3, 1.1, 1.3, 1.2; respiratory: 1.1, 1.3, 1.2, 1.1). In males, the incidences of hyaline degeneration were similar to those of the chamber controls in the olfactory epithelium (1/50, 2/50, 3/48, 1/48) and in the respiratory epithelium (4/50, 10/50, 5/48, 5/48), as were the severities (olfactory: 1.0, 1.0, 1.3, 1.0; respiratory: 1.0, 1.1, 1.4, 1.0) (Table C5). These lesions consisted of intracytoplasmic accumulation of homogenous eosinophilic material. The affected olfactory epithelium was located primarily in nasal levels I and II. These lesions were seen as brightly eosinophilic globules in the cytoplasm of affected respiratory epithelial cells and sustentacular cells, with the olfactory cells being involved most often.

Urogenital System: In the kidney, incidences of glomerulosclerosis and hydronephrosis in males exposed to 125 ppm and of chronic inflammation in males exposed to 250 ppm were significantly increased relative to the chamber controls (Tables 22 and C5). The incidences of inflammation of the preputial and prostate glands in males exposed to 250 ppm were significantly increased. Incidences of chronic inflammation and ulcer of the prepuce skin were significantly increased in males exposed to 125 or 250 ppm compared to the chamber controls, as were the incidences of inflammation of the urinary bladder. The incidence of ulcer of the transitional epithelium of the urinary bladder in males in the 125 ppm group was significantly increased. These inflammatory changes in the urinary tract are indicative of an ascending urinary tract infection and are consistent with a genito-urinary condition described in the literature as mouse urologic syndrome. In inhalation studies, the incidence of mouse urologic syndrome is particularly high in mice housed individually in wire mesh cages (Everitt *et al.*, 1988). It is likely that this condition was exacerbated by the irritative effects of 2-butoxyethanol exposure directly or by the presence of 2-butoxyethanol metabolites in urine, or by both.

TABLE 22
Incidences of Nonneoplastic Lesions of the Urogenital System in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Kidney[a]	50	50	47	50
Glomerulosclerosis[b]	4 (1.3)[c]	4 (1.3)	11* (1.3)	9 (1.4)
Hydronephrosis	1 (2.0)	0	6* (1.8)	5 (2.2)
Inflammation, Chronic Active	0	1 (2.0)	2 (2.5)	4* (3.0)
Preputial Gland	49	49	49	49
Inflammation	2 (1.0)	7 (2.3)	6 (2.3)	8* (2.1)
Prostate Gland	49	49	48	45
Inflammation	0	2 (2.0)	3 (2.3)	4* (1.8)
Skin, Prepuce	50	50	49	50
Inflammation, Chronic Active	2 (3.5)	3 (3.7)	13** (3.7)	8* (3.9)
Ulcer	0	3 (2.7)	11** (2.8)	8** (2.5)
Urinary Bladder	50	50	46	45
Inflammation	0	2 (3.5)	5* (3.4)	4* (3.8)
Transitional Epithelium, Ulcer	0	1 (3.0)	4* (2.8)	2 (3.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

GENETIC TOXICOLOGY

2-Butoxyethanol (100 to 10,000 μg/plate) did not induce mutations in any of the *Salmonella typhimurium* strains tested (TA97, TA98, TA100, TA1535, and TA1537), with or without induced hamster or rat liver S9 (Table E1; Zeiger *et al.*, 1992). In tests for induction of chromosomal damage in Chinese hamster ovary cells *in vitro*, 2-butoxyethanol induced cell cycle delay (an indication of cytotoxicity) but did not induce either sister chromatid exchanges (Table E2) or chromosomal aberrations (Table E3) with or without S9. In the chromosomal aberrations test without S9, a weakly positive response was obtained in the second trial at the highest dose tested (5,000 μg/mL), but this response was not reproduced in a third trial and the test results were concluded to be negative overall. Due to the cell cycle delay caused by 2-butoxyethanol in the trials conducted without S9, a delayed harvest was used to increase the number of cells available for analysis. *In vivo*, no induction of micronuclei was observed in polychromatic erythrocytes in bone marrow of rats or mice treated with 2-butoxyethanol (Tables E4 and E5). Rats received up to 450 mg 2-butoxyethanol/kg body weight three times at 24-hour intervals via intraperitoneal injection; two out of five rats administered 450 mg/kg died. Mice were treated by the same protocol. All mice receiving 550 mg/kg survived, whereas 100% mortality occurred in the 1,100 mg/kg dose groups.

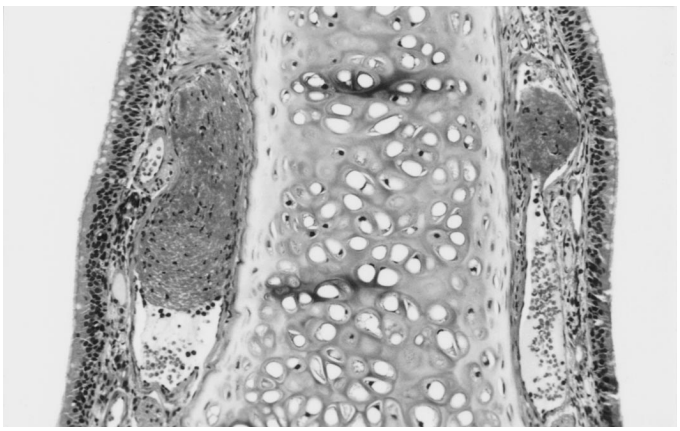

PLATE 1
Thrombosis of small caliber arteries in the submucosa of the septum at level I of the nasal cavity of a female F344/N rat killed moribund 4 days following initiation of exposure to 500 ppm 2-butoxyethanol in the 14-week inhalation study. H&E; 50×.

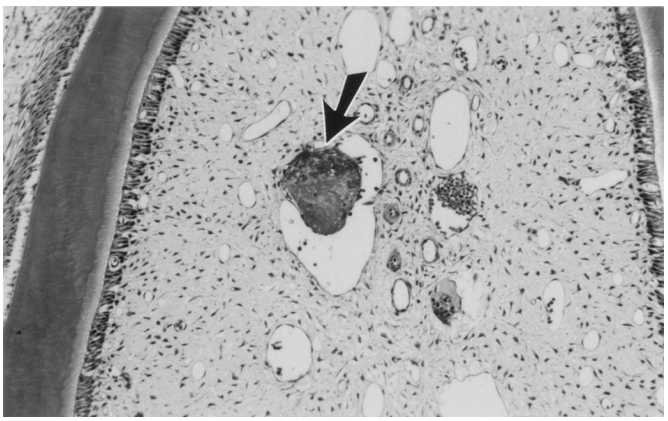

PLATE 2
Blood vessel thrombosis (arrow) in the incisors dental pulp in a female F344/N rat killed moribund 4 days following initiation of exposure to 500 ppm 2-butoxyethanol in the 14-week inhalation study. H&E; 25×.

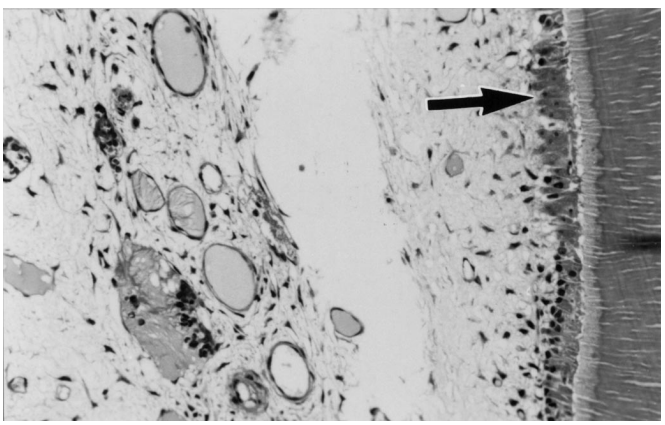

PLATE 3
Odontoblast degeneration (arrow) in the incisor tooth of a female F344/N rat killed moribund 4 days following initiation of exposure to 500 ppm 2-butoxyethanol in a 14-week inhalation study. H&E; 80×.

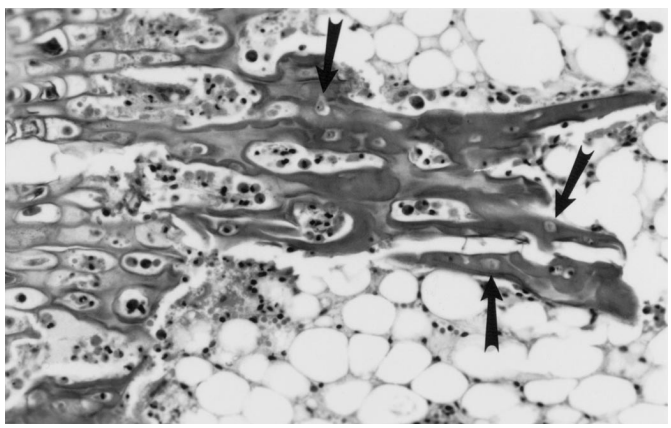

PLATE 4
Bone infarction at the level of growth plate and primary spongiosa characterized by presence of necrotic osteocytes (arrows) and necrosis of the bone-lining cells in a female F344/N rat killed moribund 4 days following initiation of exposure to 500 ppm 2-butoxyethanol in the 14-week inhalation study. H&E; 25×.

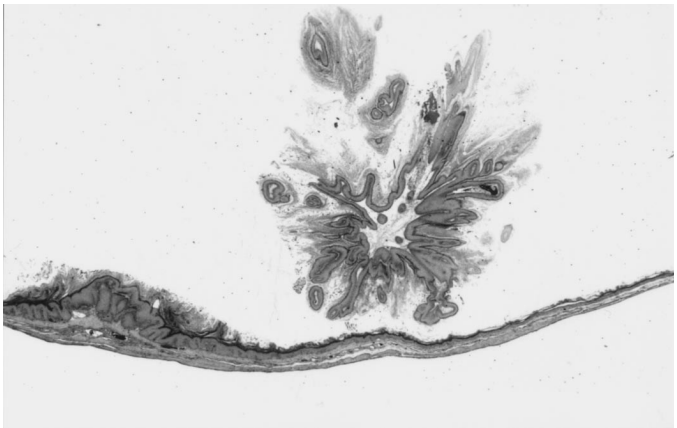

PLATE 5
Squamous cell papilloma in the forestomach of a female B6C3F$_1$ mouse exposed to 250 ppm 2-butoxyethanol by inhalation for 2 years. Note the presence of multiple branching papillary projections. H&E; 4×.

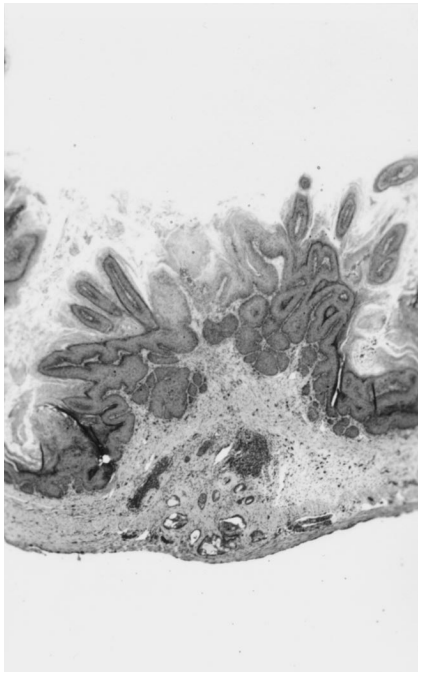

PLATE 6
Squamous cell carcinoma in the forestomach of a female B6C3F$_1$ mouse exposed to 250 ppm 2-butoxyethanol by inhalation for 2 years. H&E; 8×.

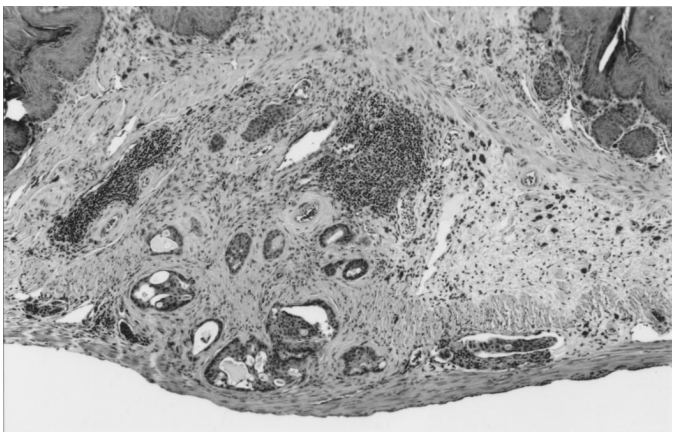

PLATE 7
Squamous cell carcinoma in the forestomach (same animal as presented in Plate 6). Note clusters of stratified squamous cells that have invaded the submucosa and muscular layer. H&E; 20×

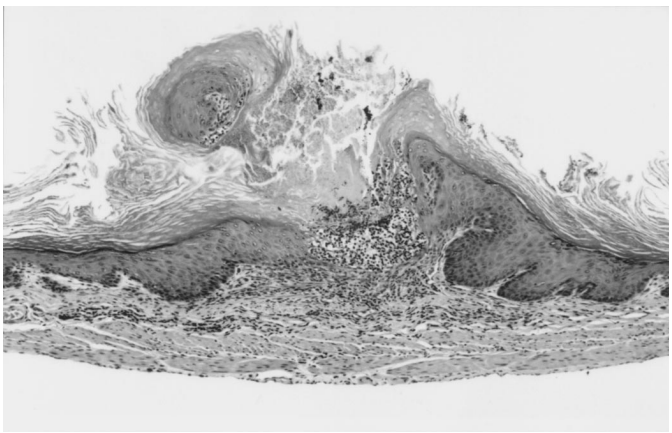

PLATE 8
Mucosal ulceration associated with moderate squamous cell hyperplasia and mild submucosal inflammation in the forestomach of a male B6C3F$_1$ mouse exposed to 250 ppm 2-butoxyethanol by inhalation for 2 years. H&E; 25×

DISCUSSION AND CONCLUSIONS

The Consumer Product Safety Commission and the United Auto Workers International Union nominated 2-butoxyethanol for study because of its use in many industrial and consumer applications, the potential exposure of workers and the general population, and the absence of chronic toxicity data. 2-Butoxyethanol was evaluated for toxicity and carcinogenicity in 14-week and 2-year studies in male and female F344/N rats and B6C3F$_1$ mice utilizing whole body inhalation as the route of exposure.

In previous studies, short-term exposure of 2-butoxyethanol to rats and mice caused hemolytic anemia and subsequent effects on the hematopoietic system by the 2-butoxyethanol metabolite 2-butoxyacetic acid (ATSDR, 1998; Ghanayem, 1996); the duration of these studies was less than 14 weeks and primarily involved rats. In the current studies, exposure of male and female rats and mice to 2-butoxyethanol for periods of 14 weeks or 2 years also caused a regenerative hemolytic anemia and subsequent effects on the hematopoietic system in rats and mice. In addition to the hemolytic effect, 2-butoxyethanol exposure for 2 years caused increases in the incidences of neoplasms and nonneoplastic lesions.

In the current studies, a concentration-dependent anemia occurred in exposed rats and mice; rats were more severely affected than mice, and females more severely than males. The anemia in rats was characterized as macrocytic, normochromic, and responsive and was evidenced by increases in mean cell volumes, no changes in mean cell hemoglobin concentrations, and an erythropoietic response demonstrated by increased reticulocyte and nucleated erythrocyte counts. However, in mice, the anemia was considered normocytic. The 14-week female rats were more sensitive to the hemolytic effects of acute 2-butoxyethanol exposure; female rats removed early had thrombosis in the blood vessels of a number of tissues, including the heart atrium, nasal septum and turbinates, liver, lung, incisors, and femur. In some tissues, the thrombosis was severe and/or associated with infarction, such as in the blood vessels of the dental pulp of the incisors, where there was odontoblast degeneration, and in the vessels of the tail vertebrae, where infarction led to necrosis and ultimate loss of the distal portion of the tail. Loss of the distal portion of the tail was also noted in prior reports (Hardin *et al.*, 1984; Nelson *et al.*, 1984; Tyl *et al.*, 1984) of inhalation, dermal, and gavage studies with 2-butoxyethanol. It is proposed that 2-butoxyethanol at concentrations of 500 ppm and greater (as used in pilot studies) produces an acute disseminated thrombosis and bone infarction in male and female rats as a result of severe acute hemolysis and reduced deformability of the erythrocytes or through anoxic damage to endothelial cells that compromises blood flow. In surviving female rats, there were lesions in the tail consistent with prior infarction, transient or complete growth arrest of the vertebrae, and, in the most severely affected animals, there was growth plate degeneration with no evidence of renewed longitudinal growth, indicating irreversible growth-plate injury. A number of effects on the hematopoietic system in rats and mice surviving to the end of the 14-week studies were consistent with the regenerative anemia, including excessive splenic extramedullary hematopoiesis and hemosiderosis, hemosiderin accumulation in hepatic Kupffer cells and renal cortical tubules, and bone marrow hyperplasia (rats). At the end of 2 years, only the pigmentation in the liver was present in exposed rats, while hematopoietic cell proliferation and pigmentation of the spleen and pigmentation in the liver occurred in exposed mice.

In the 2-year studies, 2-butoxyethanol continued to affect the circulating erythroid mass, inducing a responsive anemia. In rats, the anemia was considered mild and persisted with no apparent progression or amelioration of severity from 3 months to the final blood collection at 12 months. Although the anemia in mice, for the most part, was minimal and characterized as normocytic, normochromic, and responsive, there were changes with duration of exposure. By 12 months, the reticulocytosis was ameliorated in males and was only present in 125 ppm females. It has been demonstrated that after an initial

acute hemolytic event, rats become resistant to the hemolytic effects of 2-butoxyethanol (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995). The assumption is that the response is nonspecific and is related to the increase in the number of immature erythrocytes. As immature erythrocytes age, the increased resistance diminishes (Sivarao and Mehendale, 1995). The findings in this 2-year study also suggest that as the immature erythrocytes age, they become susceptible to the hemolytic effects of 2-butoxyethanol and are hemolyzed, which results in a persistent anemia. Apparently, there is a balance between the release of immature erythrocytes to the circulation and the aging process so that at any particular time, only a limited number of erythrocytes are susceptible to hemolysis; thus, the anemia is persistent without any dramatic changes in severity. The macrocytosis observed in rats was attributed to the number of larger reticulocytes in the circulation and is consistent with an erythropoietic response. Reticulocytosis can result in transitory increases in mean cell volumes and mean cell hemoglobin values (Duncan and Prasse, 1986); thus, the increases in mean cell volumes and mean cell hemoglobin values in rats is consistent with the reticulocytosis that occurred in response to the anemia. There were increases in bone marrow cellularity in 125 ppm female rats at all time points that were consistent with a bone-marrow response to anemia. In the 13-week drinking water study with 2-butoxyethanol, total bone marrow cell counts were increased in rats (NTP, 1993b). The bone marrow cytocentrifuge preparations, in general, revealed decreases in the myeloid to erythroid (M/E) ratios for 125 ppm males and females and 62.5 ppm females throughout the 2-year study. In the present study, the severities of the M/E ratio depressions were consistent with the persistent, responsive anemia at each time point. Unlike the rats, there were no increases in the total bone marrow cell counts or decreases in the M/E ratios of exposed mice at any time point.

As noted previously, female rats are more sensitive to the 2-butoxyethanol-induced hemolysis than are males (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; NTP, 1993b). The gender difference in rats is consistent with the kinetics observed in this 2-year study (Dill *et al.*, 1998). The hemolytic effects of 2-butoxyethanol exposure are caused by 2-butoxyacetic acid, the major metabolite of 2-butoxyethanol (Carpenter *et al.*, 1956; Bartnik *et al.*, 1987; Ghanayem, 1987a). The toxicokinetic data for male and female rats reported for the 2-year study (Dill *et al.*, 1998; Lee *et al.*, 1998) indicate that there are definite gender differences in rats, especially in the elimination of 2-butoxyacetic acid. Female rats eliminated 2-butoxyacetic acid more slowly from the blood, as indicated by the smaller elimination rate constant, longer elimination half-life, and larger area under the blood concentration-versus-time curve. In addition, female rats excreted significantly less 2-butoxyacetic acid in urine than did males; this reduced renal excretion of 2-butoxyacetic acid may be the cause of higher blood concentrations. The observed maximum blood concentrations of 2-butoxyacetic acid for females were greater than for males at each exposure concentration and time point. Therefore, female rats had considerably more 2-butoxyacetic acid in the blood at any given time point to produce a greater hemolytic effect than did males. Griffin *et al.* (1997) showed similar gender differences with male and female Sprague-Dawley rats dosed orally with 2,4-dichlorophenoxyacetic acid. Male rats were able to clear 2,4-dichlorophenoxyacetic acid from the plasma much more rapidly than were females, suggesting that female rats were exposed to a greater dose for a longer period of time than were males. The difference in clearance was attributed to a gender difference in anion transport in the kidney. The slight differences in the incidences of anemia in male and female mice may also be explained by kinetics but less clearly than for rats (Dill *et al.*, 1998). Like female rats, female mice tended to have greater blood concentrations of 2-butoxyacetic acid than did male mice. Unlike female rats, female mice excreted slightly more 2-butoxyacetic acid than did male mice. However, there was no significant difference between male and female mice in the overall rate of elimination or the half-life of 2-butoxyacetic acid.

In the 2-year rat study, survival rates were not affected by 2-butoxyethanol exposure. Mean body weights of exposed male rats were generally similar to those of the chamber controls, whereas mean body weights of 125 ppm females were slightly less than those of chamber controls for much of the study. The only potentially positive neoplastic finding in rats was a marginal increase in the incidence of benign or malignant pheochromocytomas (combined) of the adrenal gland in 125 ppm female rats; the incidences occurred with a positive trend in females. The inci-

dence (8/49) was not significantly greater than that of the chamber controls (3/50); however, the eight neoplasms observed in the 125 ppm group exceeded the overall historical control incidence in inhalation studies (6.4%) and slightly exceeded the highest incidence observed in any one inhalation control group (13%) or noninhalation control group (14%). Pheochromocytomas are relatively common in male rats, occurring with an historical control incidence of 33%. In the 125 ppm female rats, one animal had a malignant and one animal had a bilateral benign pheochromocytoma. The primary criterion used to diagnose pheochromocytomas, in contrast to medullary hyperplasia, was the presence of mild to moderate compression of the adjacent tissue. Most of the pheochromocytomas observed were small and not substantially larger than the more severe grades of adrenal gland medullary hyperplasia. In addition, the incidences of medullary hyperplasia were not significantly increased in exposed rats. Overall, the slight increase in incidences of pheochromocytoma was considered an equivocal finding and could not be attributed with certainty to 2-butoxyethanol exposure.

In the 2-year mouse study, survival rates were reduced in 125 or 250 ppm male mice. Exposed males generally had slightly lower mean body weights than chamber controls during the last 6 months of the study, whereas exposed females weighed less than chamber controls earlier in the study and had a greater reduction in weight. 2-Butoxyethanol exposure resulted in a concentration-related increase in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach. The incidence in 250 ppm females, in addition to being significantly increased compared to that in the chamber controls, exceeded the range for historical inhalation controls. Forestomach neoplasms are rare in B6C3F$_1$ mice; for the contemporary historical controls for other routes of administration, 8% is the highest incidence observed in a chamber control group. Although forestomach inflammation and necrosis were more prevalent in mice removed during the first 9 days of the 14-week study, hyperplasia and inflammation were present at the end of the study (females only), indicating that the forestomach continued to be affected by repeated 2-butoxyethanol exposure. With repeated exposure in the 2-year study, there were significant concentration-related increases in the incidences of forestomach hyperplasia and ulceration. The hyperplasia was focal and often associated with the ulceration. A direct association of neoplasia with ulceration and hyperplasia was not shown in this study although it is hypothesized that 2-butoxyethanol exposure-induced irritation caused the inflammatory and hyperplastic effects in the forestomach, and that the neoplasia was associated with a continuation of the injury/degeneration process and was, therefore, related to 2-butoxyethanol exposure. Assessment of *ras* mutations in forestomach neoplasms from male and female mice exposed to 2-butoxyethanol showed that the mutation frequency was similar to that of spontaneously occurring forestomach neoplasms (Appendix K).

In addition, there was no difference in the spectrum of *ras* mutations between males and females. The mechanism of forestomach exposure is not clear, and the role of preening or mucocilliary clearance of the respiratory tract in the exposure is unknown. A direct effect of 2-butoxyethanol exposure on the forestomach is suggested by the work of Ghanayem *et al*. (1987b); 48 hours after gavage administration of ^{14}C-labeled 2-butoxyethanol, the highest concentration of the label was in the forestomach, with approximately equal concentrations in the liver, kidney, lung, glandular stomach, and spleen. The glandular stomach contained only one-third that of the forestomach, which may indicate that for 2-butoxyethanol exposure there is a different reactivity and/or absorption in the two parts of the stomach.

For male mice exposed to 2-butoxyethanol, there were increases in the incidences of squamous cell papilloma or carcinoma (combined) of the forestomach. Although the incidences were low and not significantly increased at any concentration, the incidences in the 125 and 250 ppm mice exceeded the historical control range. Squamous cell papillomas and carcinomas (one in the 125 ppm group) are as rare in males as in females. Squamous cell carcinomas of the forestomach have not been observed in inhalation historical control male mice. For contemporary historical controls in inhalation studies, the highest number of papillomas observed was one, and for papillomas and carcinomas combined for other routes, three were seen in one untreated control group; otherwise, one was the highest observed for any route. Forestomach inflammation, necrosis, and hyperplasia were observed in mice removed early in the 14-week studies. Inflammatory and hyperplastic changes were observed at the end of the 14-week

study; however, they were more prevalent and severe in females than in males. With repeated exposure in the 2-year study, there was a significant, concentration-related increase in the incidences of forestomach hyperplasia. The incidences of ulcers were also increased in exposed males. The increased incidences of forestomach neoplasms may have been associated with 2-butoxyethanol exposure because of the rarity of these neoplasms, the increased incidences of nonneoplastic lesions supporting the neoplasia, the observation of nonneoplastic lesions in the 14-week studies, and most importantly, the fact that there was a similar, but more severe effect in female mice. The forestomach has not been a target for many inhalation studies. However, forestomach hyperplasia in male and female mice has been associated with inhalation exposure to vapors such as acetonitrile (NTP, 1996), 1,3-butadiene (NTP, 1993c), and chloroprene (NTP, 1998). Although the incidences of forestomach neoplasms were increased in exposed animals for each chemical, only the increases in the 1,3-butadiene and chloroprene studies were considered treatment related. The incidences for acetonitrile were low and did not exceed the historical control ranges.

2-Butoxyethanol exposure caused a concentration-related increase in the incidences of hemangiosarcoma of the liver in male mice that was significant in the 250 ppm group. Although the incidence was low, it exceeded the historical control incidence. For contemporary inhalation historical controls, no more than two hemangiosarcomas have been observed in any one control group, whereas as many as three have been observed in dosed feed and drinking water controls. The hemangiosarcomas were morphologically similar to spontaneously occurring hemangiosarcomas in that there were atypical endothelial cells that formed capillary and cavernous channels and solid cellular masses with local invasion. Two of the four 250 ppm mice with hemangiosarcomas also had hemangiosarcomas in other tissues; one mouse had hemangiosarcomas in the heart and bone marrow, whereas another had hemangiosarcomas in the bone marrow and spleen. The one 62.5 ppm male mouse with a hemangiosarcoma in the liver also had one in the bone marrow and one in the spleen. In animals with hemangiosarcomas at more than one site, the site of origin could not be determined by histologic evaluation. All of these tissues are involved in hematopoiesis and have been shown to be affected by the hemolytic activity of 2-butoxyethanol. Because hemangiosarcomas are rare neoplasms that were found in all exposed groups, but not in chamber controls, and because the incidence of the lesion exceeded the historical control rates for inhalation chamber controls, these neoplasms were considered related to 2-butoxyethanol exposure. The pathogenesis of this neoplasm in rodents is unknown. Although there were statistically significant increases in the incidences of hemosiderin pigmentation in hepatic Kupffer cells in male mice exposed to 125 or 250 ppm, the severities of this lesion were considered minimal. The incidences of pigmentation were increased in female mice at all exposure concentrations, and 2-butoxyethanol exposure did not result in increased incidences of hemangiosarcoma in female mice. In the four male mice exposed to 250 ppm that had hemangiosarcomas, only three of the four had hemosiderin pigmentation in the liver. An association of hemosiderin deposition in the liver and liver neoplasms (adenomas, carcinomas, or hemangiosarcomas) was not found in the 79 male and 103 female mice from the 2-year NTP studies in which the liver was a site of chemical-related neoplasms. At least for male mice, it does not appear that an accumulation of hemosiderin and possible related oxidative stress alone were the cause of the liver neoplasms. Exposure of mice to 2-butoxyethanol caused a significant concentration-related increase in the incidences of hematopoietic cell proliferation and hemosiderin deposition in the spleen; however, it did not cause increases in neoplasms in the spleen as one might expect if there were an association of hemosiderin accumulation and neoplasm response.

2-Butoxyethanol exposure caused a concentration-related increase in the incidences of hepatocellular carcinoma in male mice that was significant in the 250 ppm group. However, this incidence (43%) was within the historical control range for inhalation studies (11% to 48%). The incidences of hepatocellular adenoma or carcinoma (combined) were not increased in exposed groups of male mice and were within the historical control range for inhalation studies (20% to 86%). Hepatocellular adenomas and carcinomas are relatively common neoplasms in male $B6C3F_1$ mice; the morphology of the neoplasms was similar in exposed and chamber control mice. As discussed previously, the only exposure-related nonneoplastic effect in the liver was hemosiderin pigmentation in the Kupffer cells. In addition, in female

mice exposed to 125 or 250 ppm there were actually decreases in the incidences of hepatocellular neoplasms. In assessing potential chemical-related increases in the incidences of liver neoplasms, benign and malignant neoplasms are routinely analyzed independently and in combination. Although the independent analysis provides useful information, the most important analysis for determining potential chemical-related effects in the liver is the combined analysis of hepatocellular adenoma and carcinoma. The principal advantage of the independent analysis is for evaluation of progression to a more malignant state which may occur along with an overall increase in the incidence of neoplasms or in the absence of an overall increase (as in this study). Whether the 21 hepatocellular carcinomas in male mice exposed to 250 ppm versus the 10 in the chamber control group and the positive trend in the incidences of hepatocellular carcinoma in male mice in general were caused by exposure to 2-butoxyethanol is uncertain.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of 2-butoxyethanol in male F344/N rats exposed to 31.2, 62.5, or 125 ppm. There was *equivocal evidence of carcinogenic activity* of 2-butoxyethanol in female F344/N rats based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in male $B6C3F_1$ mice based on increased incidences of hemangiosarcoma of the liver. A marginal increase in the incidences of forestomach squamous cell papilloma and an increase in the incidences of hepatocellular carcinoma may have been exposure related. There was *some evidence of carcinogenic activity* of 2-butoxyethanol in female $B6C3F_1$ mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

Increased incidences of forestomach neoplasms in male and female mice occurred in groups in which ulceration and hyperplasia were also present.

Exposure to 2-butoxyethanol caused a mild regenerative anemia and effects secondary to the anemia.

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

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

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	25	31	24	21
Natural deaths	6	8	5	5
Survivors				
Terminal sacrifice	19	11	21	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(47)	(47)	(47)	(48)
Intestine large, cecum	(46)	(47)	(47)	(46)
Intestine small, duodenum	(46)	(47)	(49)	(49)
Intestine small, ileum	(45)	(45)	(46)	(47)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic	1 (2%)			
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Hepatocellular carcinoma		1 (2%)		1 (2%)
Hepatocellular adenoma	1 (2%)	2 (4%)		1 (2%)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, uncertain primary site	1 (2%)			
Mesentery	(8)	(6)	(15)	(8)
Hemangiosarcoma, metastatic, spleen			1 (7%)	
Sarcoma			1 (7%)	
Sarcoma, metastatic, spleen			1 (7%)	
Oral mucosa	(3)	(1)	(1)	
Gingival, fibrosarcoma		1 (100%)		
Pharyngeal, squamous cell papilloma	3 (100%)			
Pancreas	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		3 (6%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(49)	(49)	(50)	(50)
Tongue	(1)		(1)	
Squamous cell papilloma	1 (100%)		1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Adenoma	2 (4%)		1 (2%)	
Carcinoma			1 (2%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant		2 (4%)	3 (6%)	
Pheochromocytoma benign	12 (24%)	15 (30%)	9 (18%)	12 (24%)
Bilateral, pheochromocytoma benign	3 (6%)	5 (10%)	4 (8%)	4 (8%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	5 (10%)	2 (4%)	3 (6%)	3 (6%)
Adenoma, multiple			1 (2%)	1 (2%)
Carcinoma	4 (8%)	1 (2%)		3 (6%)
Pituitary gland	(49)	(49)	(48)	(47)
Pars distalis, adenoma	24 (49%)	29 (59%)	24 (50%)	25 (53%)
Thyroid gland	(50)	(46)	(48)	(48)
C-cell, adenoma	7 (14%)	3 (7%)	7 (15%)	10 (21%)
C-cell, carcinoma	1 (2%)		3 (6%)	2 (4%)
Follicular cell, adenoma	1 (2%)			3 (6%)
Follicular cell, carcinoma	1 (2%)		1 (2%)	
General Body System				
Peritoneum			(2)	(1)
Tissue NOS		(1)		
Sarcoma		1 (100%)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(46)	(47)	(50)	(43)
Adenoma	3 (7%)	1 (2%)	5 (10%)	5 (12%)
Carcinoma	5 (11%)	1 (2%)	2 (4%)	1 (2%)
Prostate	(49)	(49)	(50)	(50)
Adenoma	1 (2%)		4 (8%)	1 (2%)
Adenoma, multiple				1 (2%)
Seminal vesicle	(47)	(44)	(46)	(48)
Adenoma	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	34 (68%)	38 (76%)	36 (72%)	31 (62%)
Interstitial cell, adenoma	7 (14%)	4 (8%)	8 (16%)	10 (20%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Lymph node	(10)	(10)	(8)	(10)
Sarcoma, metastatic, skin				1 (10%)
Lymph node, bronchial	(36)	(38)	(41)	(34)
Lymph node, mandibular	(44)	(47)	(47)	(46)
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Sarcoma, metastatic, spleen			1 (2%)	
Lymph node, mediastinal	(44)	(44)	(45)	(44)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Fibroma			1 (2%)	1 (2%)
Hemangiosarcoma			1 (2%)	
Sarcoma			1 (2%)	1 (2%)
Thymus	(45)	(44)	(44)	(39)
Thymoma malignant			1 (2%)	1 (3%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Integumentary System				
Mammary gland	(44)	(40)	(44)	(45)
Carcinoma		1 (3%)		
Fibroadenoma	2 (5%)	1 (3%)	3 (7%)	1 (2%)
Fibroadenoma, multiple	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	2 (4%)	1 (2%)		
Basal cell carcinoma	2 (4%)	1 (2%)		
Keratoacanthoma	3 (6%)	3 (6%)	4 (8%)	2 (4%)
Keratoacanthoma, multiple				1 (2%)
Squamous cell papilloma	1 (2%)	1 (2%)	4 (8%)	1 (2%)
Sebaceous gland, adenoma			2 (4%)	
Subcutaneous tissue, fibroma	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Subcutaneous tissue, fibroma, multiple				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, fibrosarcoma, multiple	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, lipoma	1 (2%)	1 (2%)	2 (4%)	
Subcutaneous tissue, sarcoma				2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			1 (2%)
Skeletal muscle		(1)		
Sarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma benign				1 (2%)
Astrocytoma malignant		1 (2%)		
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Glioma malignant	2 (4%)			
Meningioma malignant		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	4 (8%)	
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)	1 (2%)
Carcinoma, metastatic, islets, pancreatic	1 (2%)			
Carcinoma, metastatic, preputial gland				1 (2%)
Hemangiosarcoma, metastatic, spleen			1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site	1 (2%)	1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal medulla		1 (2%)	1 (2%)	
Sarcoma, metastatic, skin				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Respiratory System (continued)				
Nose	(48)	(49)	(49)	(50)
Lateral wall, adenoma			1 (2%)	
Turbinate, chondroma		1 (2%)		
Pleura			(1)	
Trachea	(50)	(49)	(50)	(48)
Special Senses System				
Zymbal's gland	(1)	(1)	(2)	
Carcinoma	1 (100%)	1 (100%)	2 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Mesenchymal tumor malignant			1 (2%)	
Sarcoma		1 (2%)		
Renal tubule, adenoma	1 (2%)	2 (4%)		
Renal tubule, oncocytoma benign			1 (2%)	
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(49)	(50)	(50)	(50)
Transitional epithelium, papilloma	2 (4%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Leukemia mononuclear	29 (58%)	31 (62%)	33 (66%)	30 (60%)
Lymphoma malignant	1 (2%)			
Mesothelioma benign	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Mesothelioma malignant			3 (6%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	50
Total primary neoplasms	173	161	187	163
Total animals with benign neoplasms	49	49	49	49
Total benign neoplasms	123	114	131	119
Total animals with malignant neoplasms	40	40	41	38
Total malignant neoplasms	50	47	56	44
Total animals with metastatic neoplasms	3	3	3	2
Total metastatic neoplasms	4	3	8	3
Total animals with malignant neoplasms of uncertain primary site	2	1		

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

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

Number of Days on Study	3 5 4	5 2 0	5 2 1	5 2 9	5 5 8	5 5 8	5 6 3	5 6 4	5 6 5	5 6 8	5 9 7	6 0 9	6 1 0	6 1 7	6 3 1	6 3 8	6 4 1	6 4 2	6 4 6	6 4 8	6 4 8	6 4 9	6 7 3	6 8 3	6 8 7
Carcass ID Number	0 3 0	0 4 9	0 4 4	0 1 3	0 2 4	0 4 3	0 2 1	0 3 5	0 2 0	0 2 2	0 0 7	0 1 4	0 4 4	0 4 6	0 2 6	0 1 7	0 1 2	0 1 0	0 3 3	0 0 6	0 3 4	0 5 0	0 4 7	0 4 0	0 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	+	+	+	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																							X		
Hepatocellular adenoma																									
Sarcoma, metastatic, uncertain primary site									X																
Mesentery			+								+				+					+					+
Oral mucosa												+	+								+				
Pharyngeal, squamous cell papilloma												X	X								X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth						+							+												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X				X						X									X
Bilateral, pheochromocytoma benign														X						X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma																							X		X
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X			X	X		X				X				X	X	X	X	X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X				
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

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

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

Number of Days on Study	6 8 7	6 9 7	7 0 2	7 0 8	7 0 8	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 5	0 2 5	0 3 6	0 2 3	0 3 2	0 0 8	0 0 1	0 0 3	0 0 5	0 1 6	0 1 8	0 1 9	0 2 2	0 2 8	0 2 9	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 8	0 0 9	0 1 1	0 1 5	0 2 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular adenoma				X																						1
Sarcoma, metastatic, uncertain primary site																										1
Mesentery	+																		+	+						8
Oral mucosa																										3
Pharyngeal, squamous cell papilloma																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Tongue								+																		1
Squamous cell papilloma								X																		1
Tooth																									+	3
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X				X					X	X	X				X	X		X					12
Bilateral, pheochromocytoma benign					X																					3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X				X		X												X							5
Carcinoma									X		X															4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Pars distalis, adenoma	X	X	X	X	X				X	X							X	X	X			X				24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X										X	X	X				X	X							7
C-cell, carcinoma													X													1
Follicular cell, adenoma																	X									1
Follicular cell, carcinoma																				X						1
General Body System																										
None																										

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

Number of Days on Study	3 5 4	5 2 0	5 2 1	5 2 9	5 5 8	5 5 8	5 6 3	5 6 4	5 6 5	5 6 8	5 9 7	6 0 9	6 1 0	6 1 7	6 3 1	6 3 8	6 4 1	6 4 2	6 4 6	6 4 8	6 4 8	6 4 9	6 7 3	6 8 3	6 8 7
Carcass ID Number	0 3 0	0 4 9	0 4 4	0 1 3	0 2 4	0 4 3	0 2 1	0 3 5	0 2 0	0 0 2	0 0 7	0 1 4	0 0 4	0 4 6	0 2 6	0 1 7	1 1 2	1 1 0	1 3 3	0 0 6	3 4	5 0	4 7	4 0	3 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma													X		X										
Carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X		X		X		X	X		X	X	X				X		X		X
Interstitial cell, adenoma				X							X								X	X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+		+	+						+	+									
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+	M	+	+	M	M	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																	X								X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Keratoacanthoma				X																					
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma, multiple												X													
Subcutaneous tissue, hemangiosarcoma																							X		
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																			X						

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

Number of Days on Study	6 8 7	6 9 7	7 0 2	7 0 8	7 0 8	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 5	0 2 5	0 3 6	0 2 3	0 3 2	0 0 8	0 0 1	0 0 3	0 0 5	0 1 6	0 1 8	0 1 9	0 2 2	0 2 8	0 2 9	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 8	0 9 0	0 1 1	0 1 5	0 2 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	46
Adenoma								X																		3
Carcinoma		X		X		X												X								5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Adenoma													X													1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	47
Adenoma																						X				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	34
Interstitial cell, adenoma			X		X																X					7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+				+			+								+						10
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	36
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	44
Fibroadenoma																										2
Fibroadenoma, multiple									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																X			X							2
Basal cell carcinoma															X						X					2
Keratoacanthoma										X								X								3
Squamous cell papilloma					X																					1
Subcutaneous tissue, fibroma																			X							2
Subcutaneous tissue, fibrosarcoma, multiple																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, lipoma																	X									1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma	X																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant											X															2

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

Number of Days on Study	3 5 4	5 2 0	5 2 1	5 2 9	5 5 8	5 5 8	5 6 3	5 6 4	5 6 5	5 6 8	5 9 7	6 0 9	6 1 0	6 1 7	6 3 1	6 3 8	6 4 1	6 4 2	6 4 6	6 4 8	6 4 8	6 4 9	6 7 3	6 8 3	6 8 7
Carcass ID Number	0 3 0	0 4 9	0 4 4	0 1 3	0 2 4	0 4 3	0 2 1	0 3 5	0 2 0	0 0 2	0 0 7	0 1 4	0 0 4	0 4 6	0 2 6	0 1 7	0 1 2	0 1 0	0 3 3	0 0 6	0 3 4	0 5 0	0 4 7	0 4 0	0 3 1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, islets, pancreatic																							X		
Histiocytic sarcoma																X									
Osteosarcoma, metastatic, uncertain primary site																									
Nose	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye														+											
Zymbal's gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									X
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																X									
Leukemia mononuclear	X			X	X	X		X	X		X		X	X	X	X	X	X		X					X
Lymphoma malignant										X															
Mesothelioma benign											X														

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

Number of Days on Study	6 8 7	6 9 7	7 0 2	7 0 8	7 0 8	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 5	0 2 5	0 3 6	0 2 3	0 3 2	0 0 8	0 0 1	0 0 3	0 0 5	0 1 6	0 1 8	0 1 9	0 2 2	0 2 8	0 2 9	0 3 7	0 3 8	0 3 9	0 4 1	0 4 2	0 4 8	0 0 9	0 1 1	0 1 5	0 2 7	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									1
Carcinoma, metastatic, islets, pancreatic																										1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, uncertain primary site																									X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye										+																2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma			X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Transitional epithelium, papilloma													X													2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X			X	X	X	X	X	X		X	X			X	X		X	X			X			29
Lymphoma malignant																										1
Mesothelioma benign																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	4 6 5	4 7 9	5 2 9	5 3 3	5 3 3	5 3 6	5 4 4	5 6 1	5 7 5	5 7 6	5 7 9	5 9 2	6 1 0	6 1 7	6 1 7	6 2 0	6 2 7	6 3 0	6 3 3	6 3 8	6 4 6	6 4 9	6 5 2	6 5 2	6 5 2
Carcass ID Number	2 3 6	2 5 0	2 3 7	2 2 4	2 4 0	2 4 5	2 3 2	2 4 7	2 1 2	2 0 8	2 3 9	2 1 8	2 4 2	2 0 5	2 2 2	2 2 9	2 1 4	2 2 6	2 0 2	2 0 4	2 4 3	2 0 1	2 1 7	2 1 9	2 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma														X											
Mesentery					+											+								+	
Oral mucosa	+																								
Gingival, fibrosarcoma	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																				+					
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																		X							
Pheochromocytoma benign					X	X														X					
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Carcinoma																									
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X		X		X					X	X	X	X		X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A
C-cell, adenoma					X																				
General Body System																									
Tissue NOS														+											
Sarcoma														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	659	664	666	674	677	688	693	702	704	704	716	722	723	723	729	729	729	729	729	729	729	729	729	730	730	
Carcass ID Number	221	227	244	213	230	238	207	234	203	215	246	216	211	225	206	209	220	223	238	235	241	248	249	210	231	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma							X																			1
Hepatocellular adenoma															X											2
Mesentery			+					+										+								6
Oral mucosa																										1
Gingival, fibrosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Blood vessel												+		+												2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant													X													2
Pheochromocytoma benign			X			X	X			X	X	X	X					X	X		X		X		X	15
Bilateral, pheochromocytoma benign		X		X										X										X		5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	2
Carcinoma															X											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X	X		X			X				X		X	X	X			X	X	X	29
Thyroid gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell, adenoma													X			X										3
General Body System																										
Tissue NOS																										1
Sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	4 6 5	4 7 9	5 2 9	5 3 3	5 3 3	5 3 6	5 4 4	5 6 1	5 7 5	5 7 6	5 7 9	5 9 2	6 1 0	6 1 7	6 1 7	6 2 0	6 2 7	6 3 0	6 3 3	6 3 8	6 4 6	6 4 9	6 5 2	6 5 2	6 5 2
Carcass ID Number	2 3 6	2 5 0	2 3 7	2 4 4	2 4 0	2 4 5	2 3 2	2 4 7	2 1 2	2 0 8	2 3 9	2 1 8	2 4 2	2 0 5	2 2 2	2 2 9	2 1 4	2 2 6	2 0 2	2 0 4	2 4 3	2 0 1	2 1 7	2 1 9	2 3 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	+	+	A
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X			X		X	X	X		X		X	X	X	X	X	X	X		X		X
Interstitial cell, adenoma												X		X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+		+						+				+				+				
Lymph node, bronchial	M	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																				X					
Keratoacanthoma											X												X		
Squamous cell papilloma																									
Subcutaneous tissue, fibroma															X										
Subcutaneous tissue, lipoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, Zymbal's gland																									X
Meningioma malignant		X																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	6 5 9	6 6 4	6 6 6	6 7 4	6 7 7	6 8 8	6 9 3	7 0 2	7 0 4	7 0 4	7 1 6	7 2 2	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	2 2 1	2 2 7	2 4 4	2 1 3	2 3 0	2 3 8	2 0 7	2 3 4	2 0 3	2 1 5	2 4 6	2 1 6	2 1 1	2 2 5	2 0 6	2 0 9	2 2 0	2 2 3	2 2 8	2 3 5	2 4 1	2 4 8	2 4 9	2 1 0	2 3 1	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																	X								1
Carcinoma																				X					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	38
Interstitial cell, adenoma						X					X														4
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+						+			+				+										10
Lymph node, bronchial	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	38
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Integumentary System																									
Mammary gland	+	+	M	+	+	+	M	+	+	M	+	+	M	M	+	I	+	+	+	M	+	+	+	+	+	40
Carcinoma																								X		1
Fibroadenoma					X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma															X										1
Basal cell carcinoma																									1
Keratoacanthoma			X																						3
Squamous cell papilloma														X											1
Subcutaneous tissue, fibroma			X																						2
Subcutaneous tissue, lipoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																								+	1
Sarcoma																								X	1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																				X					1
Carcinoma, metastatic, Zymbal's gland																									1
Meningioma malignant																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	465	479	529	533	533	536	544	561	575	576	579	592	610	617	617	620	627	630	633	638	646	649	652	652	652
Carcass ID Number	236	250	307	244	400	445	352	417	512	088	399	181	422	050	222	299	141	262	020	044	434	010	177	199	263
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, uncertain primary site																									
Pheochromocytoma malignant, metastatic, adrenal medulla																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Turbinate, chondroma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland																									+
Carcinoma																									X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Renal tubule, adenoma						X																			
Transitional epithelium, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X		X	X	X	X	X			X	X	X	X		X		X	X	X
Mesothelioma benign																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	6 5 9	6 6 4	6 6 6	6 7 4	6 7 7	6 8 8	6 9 3	7 0 2	7 0 4	7 0 4	7 1 6	7 2 2	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	2 2 1	2 2 7	2 4 4	2 1 3	2 3 0	2 3 8	2 0 7	2 3 4	2 0 3	2 1 5	2 4 6	2 1 6	2 1 1	2 2 5	2 0 6	2 0 9	2 2 0	2 2 3	2 2 8	2 3 5	2 4 1	2 4 8	2 4 9	2 1 0	2 3 1	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X	X						2
Alveolar/bronchiolar carcinoma														X												1
Osteosarcoma, metastatic, uncertain primary site		X																								1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Turbinate, chondroma													X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma									X																	1
Renal tubule, adenoma								X																		2
Transitional epithelium, carcinoma																				X						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X		X		X		X	X	X	X		X	X			X		X		X	X		31
Mesothelioma benign																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 0 8	7 0 8	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 0 7	4 3 6	4 1 1	4 2 4	4 0 5	4 0 8	4 2 1	4 2 5	4 2 6	4 2 9	4 3 0	4 3 3	4 3 7	4 3 9	4 4 2	4 4 4	4 4 5	4 4 7	4 4 9	4 5 0	4 0 1	4 0 2	4 1 3	4 4 3	4 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen			X																							1
Histiocytic sarcoma										X																1
Mesentery		+	+	+									+						+	+					+	15
Hemangiosarcoma, metastatic, spleen			X																							1
Sarcoma				X																						1
Sarcoma, metastatic, spleen		X																								1
Oral mucosa															+											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																X		X			3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+																			1
Squamous cell papilloma							X																			1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																			X							3
Pheochromocytoma benign				X						X		X		X				X								9
Bilateral, pheochromocytoma benign											X														X	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																			X			3
Adenoma, multiple														X												1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	47
Pituitary gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X	X	X		X	X				X				X		X		X		X		X	X	X		24
Thyroid gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma						X											X		X		X	X				7
C-cell, carcinoma																			X				X			3
Follicular cell, carcinoma															X											1
General Body System																										
Peritoneum								+																		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	340	370	387	461	472	484	542	549	561	565	584	612	617	622	627	644	658	666	666	673	677	688	694	701	703
Carcass ID Number	416	420	440	403	409	432	428	415	434	431	414	412	410	406	404	423	441	418	448	417	438	427	419	435	422
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X																X							X
Carcinoma																								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X		X	X			X	X		X			X	X	X			X	X		X	X
Interstitial cell, adenoma		X	X						X			X		X					X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+		+							+					+			+	+
Lymph node, bronchial	+	+	M	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Sarcoma, metastatic, spleen																									
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Hemangiosarcoma																									
Sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Fibroadenoma										X															X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma	X											X				X									
Squamous cell papilloma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 0 8	7 0 8	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 0 7	4 3 6	4 1 1	4 2 4	4 0 5	4 0 8	4 2 1	4 2 5	4 2 6	4 2 9	4 3 0	4 3 3	4 3 7	4 3 9	4 4 2	4 4 4	4 4 5	4 4 7	4 4 9	4 5 0	4 0 1	4 0 2	4 1 3	4 4 3	4 4 6	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X														X			5
Carcinoma															X											2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X														X	X		X							4
Seminal vesicle	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	36
Interstitial cell, adenoma																					X	X				8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																								+		8
Lymph node, bronchial	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen			X																							1
Sarcoma, metastatic, spleen		X																								1
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	45
Hemangiosarcoma, metastatic, spleen			X																							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma							X																			1
Hemangiosarcoma			X																							1
Sarcoma		X																								1
Thymus	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Thymoma malignant		X																								1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	44
Fibroadenoma							X																			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																							X			4
Squamous cell papilloma							X			X		X						X								4
Sebaceous gland, adenoma	X																								X	2
Subcutaneous tissue, fibroma													X										X			2
Subcutaneous tissue, fibrosarcoma															X											1
Subcutaneous tissue, lipoma														X		X										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	340	370	387	461	472	484	542	544	561	565	584	612	617	622	627	644	658	666	666	673	677	688	694	701	703
Carcass ID Number	41160	42000	44003	40409	40932	43628	42815	41354	43311	43514	41142	41120	41106	40644	40023	42341	41218	44886	41317	43878	42719	41959	43552	42292
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma																									
Hemangiosarcoma, metastatic, spleen																									
Histiocytic sarcoma																									
Pheochromocytoma malignant, metastatic, adrenal medulla															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lateral wall, adenoma																			X						
Pleura																		+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesenchymal tumor malignant																									
Renal tubule, oncocytoma benign																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear			X			X	X		X		X	X	X		X	X	X		X	X	X	X	X	X	X
Mesothelioma benign																									
Mesothelioma malignant				X														X							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 0 8	7 0 8	7 1 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 0 7	4 3 6	4 1 1	4 2 4	4 0 5	4 0 8	4 2 1	4 2 5	4 2 6	4 2 9	4 3 0	4 3 3	4 3 7	4 3 9	4 4 2	4 4 4	4 4 5	4 4 7	4 4 9	4 5 0	4 0 1	4 0 2	4 1 3	4 4 3	4 4 6	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X		X		X											4
Alveolar/bronchiolar carcinoma																		X								1
Hemangiosarcoma, metastatic, spleen			X																							1
Histiocytic sarcoma										X																1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lateral wall, adenoma																										1
Pleura																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+															+							2
Zymbal's gland				+																						2
Carcinoma				X																						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Mesenchymal tumor malignant																									X	1
Renal tubule, oncocytoma benign																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Leukemia mononuclear	X			X	X			X	X		X		X	X	X		X	X			X	X	X	X	X	33
Mesothelioma benign																						X				1
Mesothelioma malignant								X																		3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	638	603	005	006	009	014	023	024	026	032	035	040	041	043	046	047	048	050	113	120	222	233	236	239	249	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma													X													1
Mesentery	+		+	+											+				+					+		8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X							X		X			X								X	X		X	X	12
Bilateral, pheochromocytoma benign		X					X																			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X										X												3
Adenoma, multiple																			X							1
Carcinoma			X		X						X															3
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Pars distalis, adenoma		X		X			X	X		X	X	X	X	X				X			X	X		X	X	25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma		X		X	X				X	X			X						X				X	X		10
C-cell, carcinoma					X			X																		2
Follicular cell, adenoma																X		X			X					3
General Body System																										
Peritoneum																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	M	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	43
Adenoma	X					X											X									5
Carcinoma																									X	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X																							1
Adenoma, multiple				X																						1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		31
Interstitial cell, adenoma							X																X	X		10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	4 4 4	4 8 1	4 9 5	5 0 8	5 1 7	5 1 9	5 3 4	5 7 5	5 7 6	5 8 9	6 1 1	6 1 7	6 2 8	6 3 8	6 4 7	6 5 2	6 5 4	6 5 9	6 6 6	6 9 0	6 9 4	6 9 5	7 0 3	7 0 8	7 1 8
Carcass ID Number	6 0 1	6 2 5	6 1 2	6 0 7	6 4 4	6 3 1	6 3 4	6 1 5	6 1 8	6 3 0	6 1 1	6 1 6	6 1 0	6 0 8	6 1 9	6 0 4	6 4 5	6 4 2	6 0 2	6 2 8	6 3 7	6 1 7	6 2 9	6 2 7	6 2 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Lymph node	+	+						+	+			+		+	+	+									
Sarcoma, metastatic, skin									X																
Lymph node, bronchial	+	+	+	+	+	M	+	+	M	M	+	+	M	M	M	+	+	+	M	M	+	+	M	I	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Sarcoma																									
Thymus	+	M	+	+	+	+	+	M	+	M	+	M	+	+	+	+	M	+	M	+	+	+	M	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma												X													
Keratoacanthoma, multiple																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma														X											
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, sarcoma									X					X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign															X										
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, preputial gland																									
Sarcoma, metastatic, skin									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X				X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mesothelioma benign																				X					
Mesothelioma malignant										X															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	723	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	63 8	60 3	60 5	60 6	60 9	61 4	62 3	62 4	62 6	63 2	63 5	64 0	64 1	64 3	64 6	64 7	64 8	65 0	61 3	62 0	62 2	63 3	63 6	63 9	64 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																+			+							10
Sarcoma, metastatic, skin																										1
Lymph node, bronchial	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	34
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																				X						1
Sarcoma																	X									1
Thymus	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	39
Thymoma malignant																				X						1
Integumentary System																										
Mammary gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Fibroadenoma																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																	X									2
Keratoacanthoma, multiple																								X		1
Squamous cell papilloma																							X			1
Subcutaneous tissue, fibroma									X																X	3
Subcutaneous tissue, fibroma, multiple											X															1
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma	X																									1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma benign																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma			X																							1
Carcinoma, metastatic, preputial gland																									X	1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Eye							+																			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X			X				X		X	X	X		X			X	X	X	X	30
Mesothelioma benign																										1
Mesothelioma malignant																										1

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	15/50 (30%)	20/50 (40%)	13/49 (27%)	16/50 (32%)
Adjusted rate[b]	36.5%	50.3%	32.8%	38.3%
Terminal rate[c]	7/19 (37%)	6/11 (55%)	6/21 (29%)	9/24 (38%)
First incidence (days)	558	533	658	611
Poly-3 test[d]	P=0.424N	P=0.140	P=0.452N	P=0.522
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/49 (6%)	0/50 (0%)
Adjusted rate	0.0%	5.4%	7.7%	0.0%
Terminal rate	0/19 (0%)	0/11 (0%)	1/21 (5%)	0/24 (0%)
First incidence (days)	—[e]	630	622	—
Poly-3 test	P=0.506N	P=0.227	P=0.119	—[f]
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	15/50 (30%)	21/50 (42%)	15/49 (31%)	16/50 (32%)
Adjusted rate	36.5%	52.4%	37.5%	38.3%
Terminal rate	7/19 (37%)	6/11 (55%)	7/21 (33%)	9/24 (38%)
First incidence (days)	558	533	622	611
Poly-3 test	P=0.413N	P=0.100	P=0.557	P=0.522
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	2.6%	8.1%	0.0%	4.9%
Terminal rate	0/19 (0%)	1/11 (9%)	0/21 (0%)	1/24 (4%)
First incidence (days)	708	617	—	666
Poly-3 test	P=0.572	P=0.290	P=0.500N	P=0.516
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.6%	5.5%	10.1%	0.0%
Terminal rate	1/19 (5%)	2/11 (18%)	3/21 (14%)	0/24 (0%)
First incidence (days)	729 (T)	729 (T)	472	—
Poly-3 test	P=0.341N	P=0.482	P=0.183	P=0.492N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	5/50 (10%)	1/50 (2%)
Adjusted rate	2.6%	8.2%	12.7%	2.5%
Terminal rate	1/19 (5%)	2/11 (18%)	4/21 (19%)	1/24 (4%)
First incidence (days)	729 (T)	723	472	729 (T)
Poly-3 test	P=0.508N	P=0.285	P=0.104	P=0.752N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	7.7%	2.7%	7.6%	2.5%
Terminal rate	1/19 (5%)	0/11 (0%)	1/21 (5%)	1/24 (4%)
First incidence (days)	641	677	565	729 (T)
Poly-3 test	P=0.289N	P=0.325N	P=0.661N	P=0.294N

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	7.7%	5.4%	7.6%	2.5%
Terminal rate	1/19 (5%)	1/11 (9%)	1/21 (5%)	1/24 (4%)
First incidence (days)	641	677	565	729 (T)
Poly-3 test	P=0.242N	P=0.527N	P=0.661N	P=0.294N
Oral Cavity (Oral Mucosa): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.5%	0.0%	0.0%	0.0%
Terminal rate	0/19 (0%)	0/11 (0%)	0/21 (0%)	0/24 (0%)
First incidence (days)	609	—	—	—
Poly-3 test	P=0.041N	P=0.133N	P=0.123N	P=0.115N
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma				
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	10.1%	0.0%	2.6%	0.0%
Terminal rate	1/19 (5%)	0/11 (0%)	1/21 (5%)	0/24 (0%)
First incidence (days)	609	—	729 (T)	—
Poly-3 test	P=0.032N	P=0.070N	P=0.185N	P=0.058N
Pancreas: Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.6%	0.0%	7.8%	0.0%
Terminal rate	1/19 (5%)	0/11 (0%)	3/21 (14%)	0/24 (0%)
First incidence (days)	729 (T)	—	729 (T)	—
Poly-3 test	P=0.470N	P=0.510N	P=0.304	P=0.492N
Pancreatic Islets: Adenoma				
Overall rate	5/50 (10%)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted rate	12.7%	5.4%	10.3%	9.9%
Terminal rate	2/19 (11%)	0/11 (0%)	2/21 (10%)	3/24 (13%)
First incidence (days)	610	561	694	654
Poly-3 test	P=0.524N	P=0.234N	P=0.507N	P=0.480N
Pancreatic Islets: Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	10.3%	2.7%	0.0%	7.5%
Terminal rate	2/19 (11%)	1/11 (9%)	0/21 (0%)	3/24 (13%)
First incidence (days)	673	729 (T)	—	729 (T)
Poly-3 test	P=0.483N	P=0.195N	P=0.060N	P=0.483N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	9/50 (18%)	3/50 (6%)	4/50 (8%)	7/50 (14%)
Adjusted rate	22.7%	8.0%	10.3%	17.3%
Terminal rate	4/19 (21%)	1/11 (9%)	2/21 (10%)	6/24 (25%)
First incidence (days)	610	561	694	654
Poly-3 test	P=0.452N	P=0.069N	P=0.117N	P=0.371N

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	24/49 (49%)	29/49 (59%)	24/48 (50%)	25/47 (53%)
Adjusted rate	55.2%	65.0%	55.8%	59.0%
Terminal rate	6/18 (33%)	7/11 (64%)	10/20 (50%)	14/23 (61%)
First incidence (days)	520	479	340	495
Poly-3 test	P=0.522	P=0.223	P=0.562	P=0.442
Preputial Gland: Adenoma				
Overall rate	3/46 (7%)	1/47 (2%)	5/50 (10%)	5/43 (12%)
Adjusted rate	8.4%	2.9%	12.5%	14.4%
Terminal rate	1/16 (6%)	1/11 (9%)	2/21 (10%)	2/19 (11%)
First incidence (days)	610	729 (T)	370	519
Poly-3 test	P=0.141	P=0.314N	P=0.417	P=0.336
Preputial Gland: Carcinoma				
Overall rate	5/46 (11%)	1/47 (2%)	2/50 (4%)	1/43 (2%)
Adjusted rate	14.0%	2.9%	5.2%	3.0%
Terminal rate	1/16 (6%)	1/11 (9%)	1/21 (5%)	1/19 (5%)
First incidence (days)	564	729 (T)	701	729 (T)
Poly-3 test	P=0.089N	P=0.104N	P=0.180N	P=0.112N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	8/46 (17%)	2/47 (4%)	7/50 (14%)	6/43 (14%)
Adjusted rate	21.9%	5.8%	17.5%	17.3%
Terminal rate	2/16 (13%)	2/11 (18%)	3/21 (14%)	3/19 (16%)
First incidence (days)	564	729 (T)	370	519
Poly-3 test	P=0.559N	P=0.049N	P=0.421N	P=0.425N
Prostate Gland: Adenoma				
Overall rate	1/49 (2%)	0/49 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.7%	0.0%	10.3%	5.0%
Terminal rate	1/18 (6%)	0/11 (0%)	3/21 (14%)	2/24 (8%)
First incidence (days)	729 (T)	—	708	729 (T)
Poly-3 test	P=0.275	P=0.508N	P=0.186	P=0.524
Skin: Squamous Cell Papilloma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.6%	2.7%	10.3%	2.5%
Terminal rate	0/19 (0%)	0/11 (0%)	4/21 (19%)	1/24 (4%)
First incidence (days)	708	723	729 (T)	729 (T)
Poly-3 test	P=0.563	P=0.749	P=0.176	P=0.753N
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	7.6%	8.0%	9.9%	7.4%
Terminal rate	2/19 (11%)	0/11 (0%)	1/21 (5%)	2/24 (8%)
First incidence (days)	529	579	340	617
Poly-3 test	P=0.567N	P=0.645	P=0.515	P=0.647N

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	4/50 (8%)	4/50 (8%)	8/50 (16%)	4/50 (8%)
Adjusted rate	10.2%	10.6%	19.8%	9.8%
Terminal rate	2/19 (11%)	0/11 (0%)	5/21 (24%)	3/24 (13%)
First incidence (days)	529	579	340	617
Poly-3 test	P=0.544	P=0.622	P=0.184	P=0.627N
Skin: Basal Cell Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rate	10.4%	5.4%	0.0%	0.0%
Terminal rate	4/19 (21%)	1/11 (9%)	0/21 (0%)	0/24 (0%)
First incidence (days)	729 (T)	638	—	—
Poly-3 test	P=0.015N	P=0.355N	P=0.059N	P=0.054N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma				
Overall rate	8/50 (16%)	6/50 (12%)	8/50 (16%)	4/50 (8%)
Adjusted rate	20.3%	15.8%	19.8%	9.8%
Terminal rate	6/19 (32%)	1/11 (9%)	5/21 (24%)	3/24 (13%)
First incidence (days)	529	579	340	617
Poly-3 test	P=0.145N	P=0.410N	P=0.590N	P=0.156N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	5.1%	5.4%	5.2%	9.9%
Terminal rate	1/19 (5%)	0/11 (0%)	2/21 (10%)	3/24 (13%)
First incidence (days)	646	617	729 (T)	638
Poly-3 test	P=0.241	P=0.680	P=0.693	P=0.355
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	7.6%	5.4%	7.8%	9.9%
Terminal rate	1/19 (5%)	0/11 (0%)	3/21 (14%)	3/24 (13%)
First incidence (days)	609	617	729 (T)	638
Poly-3 test	P=0.369	P=0.525N	P=0.656	P=0.517
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	5/50 (10%)
Adjusted rate	7.6%	5.4%	7.8%	12.2%
Terminal rate	1/19 (5%)	0/11 (0%)	3/21 (14%)	3/24 (13%)
First incidence (days)	609	617	729 (T)	576
Poly-3 test	P=0.229	P=0.525N	P=0.656	P=0.379
Testes: Adenoma				
Overall rate	41/50 (82%)	42/50 (84%)	44/50 (88%)	41/50 (82%)
Adjusted rate	89.9%	92.1%	93.4%	88.2%
Terminal rate	19/19 (100%)	11/11 (100%)	21/21 (100%)	22/24 (92%)
First incidence (days)	529	533	370	481
Poly-3 test	P=0.399N	P=0.501	P=0.386	P=0.529N

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/50 (14%)	3/46 (7%)	7/48 (15%)	10/48 (21%)
Adjusted rate	17.9%	8.7%	18.4%	25.5%
Terminal rate	5/19 (26%)	1/11 (9%)	5/21 (24%)	9/24 (38%)
First incidence (days)	648	533	658	611
Poly-3 test	P=0.120	P=0.204N	P=0.597	P=0.292
Thyroid Gland (C-cell): Carcinoma				
Overall rate	1/50 (2%)	0/46 (0%)	3/48 (6%)	2/48 (4%)
Adjusted rate	2.6%	0.0%	8.0%	5.2%
Terminal rate	1/19 (5%)	0/11 (0%)	2/21 (10%)	2/24 (8%)
First incidence (days)	729 (T)	—	703	729 (T)
Poly-3 test	P=0.263	P=0.525N	P=0.295	P=0.501
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	7/50 (14%)	3/46 (7%)	9/48 (19%)	11/48 (23%)
Adjusted rate	17.9%	8.7%	23.6%	28.1%
Terminal rate	5/19 (26%)	1/11 (9%)	6/21 (29%)	10/24 (42%)
First incidence (days)	648	533	658	611
Poly-3 test	P=0.066	P=0.204N	P=0.370	P=0.208
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	0/46 (0%)	0/48 (0%)	3/48 (6%)
Adjusted rate	2.6%	0.0%	0.0%	7.7%
Terminal rate	1/19 (5%)	0/11 (0%)	0/21 (0%)	3/24 (13%)
First incidence (days)	729 (T)	—	—	729 (T)
Poly-3 test	P=0.089	P=0.525N	P=0.505N	P=0.305
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/46 (0%)	1/48 (2%)	3/48 (6%)
Adjusted rate	5.2%	0.0%	2.7%	7.7%
Terminal rate	2/19 (11%)	0/11 (0%)	1/21 (5%)	3/24 (13%)
First incidence (days)	729 (T)	—	729 (T)	729 (T)
Poly-3 test	P=0.255	P=0.265N	P=0.509N	P=0.501
All Organs: Benign or Malignant Mesothelioma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.6%	2.7%	10.1%	4.9%
Terminal rate	0/19 (0%)	0/11 (0%)	2/21 (10%)	0/24 (0%)
First incidence (days)	597	652	461	589
Poly-3 test	P=0.349	P=0.749	P=0.181	P=0.516
All Organs: Mononuclear Cell Leukemia				
Overall rate	29/50 (58%)	31/50 (62%)	33/50 (66%)	30/50 (60%)
Adjusted rate	63.6%	69.4%	73.5%	64.6%
Terminal rate	11/19 (58%)	6/11 (55%)	14/21 (67%)	11/24 (46%)
First incidence (days)	354	533	387	444
Poly-3 test	P=0.541	P=0.352	P=0.204	P=0.547

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	99.8%	99.5%	98.7%	99.5%
Terminal rate	19/19 (100%)	11/11 (100%)	21/21 (100%)	24/24 (100%)
First incidence (days)	520	479	340	481
Poly-3 test	P=0.748N	P=0.999N	P=0.771N	P=1.000N
All Organs: Malignant Neoplasms				
Overall rate	41/50 (82%)	40/50 (80%)	41/50 (82%)	38/50 (76%)
Adjusted rate	85.5%	84.9%	88.4%	80.1%
Terminal rate	16/19 (84%)	8/11 (73%)	17/21 (81%)	16/24 (67%)
First incidence (days)	354	465	387	444
Poly-3 test	P=0.270N	P=0.588N	P=0.455	P=0.328N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	19/19 (100%)	11/11 (100%)	21/21 (100%)	24/24 (100%)
First incidence (days)	354	465	340	444
Poly-3 test	—	—	—	—

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, pancreas, pancreatic islets, pituitary gland, preputial gland, prostate gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	25	31	24	21
Natural deaths	6	8	5	5
Survivors				
Terminal sacrifice	19	11	21	24
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(47)	(47)	(47)	(48)
Parasite metazoan	4 (9%)	4 (9%)	4 (9%)	4 (8%)
Intestine large, rectum	(46)	(47)	(48)	(47)
Parasite metazoan	1 (2%)	2 (4%)	6 (13%)	3 (6%)
Perforation			1 (2%)	
Intestine large, cecum	(46)	(47)	(47)	(46)
Necrosis				1 (2%)
Parasite metazoan	6 (13%)	7 (15%)	4 (9%)	5 (11%)
Intestine small, duodenum	(46)	(47)	(49)	(49)
Necrosis		1 (2%)		
Intestine small, ileum	(45)	(45)	(46)	(47)
Inflammation, acute				1 (2%)
Inflammation, chronic active				1 (2%)
Parasite metazoan	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Basophilic focus	26 (52%)	21 (42%)	25 (50%)	27 (54%)
Clear cell focus	10 (20%)	7 (14%)	13 (26%)	9 (18%)
Cyst	1 (2%)			
Degeneration, cystic	7 (14%)	6 (12%)	15 (30%)	6 (12%)
Eosinophilic focus	6 (12%)	4 (8%)	3 (6%)	4 (8%)
Fatty change	7 (14%)	10 (20%)	6 (12%)	3 (6%)
Hematopoietic cell proliferation	2 (4%)	3 (6%)		1 (2%)
Hepatodiaphragmatic nodule	1 (2%)	2 (4%)		1 (2%)
Mixed cell focus		1 (2%)	1 (2%)	1 (2%)
Necrosis	7 (14%)	9 (18%)	4 (8%)	11 (22%)
Regeneration	1 (2%)		4 (8%)	
Thrombosis	1 (2%)		1 (2%)	1 (2%)
Bile duct, hyperplasia	28 (56%)	29 (58%)	30 (60%)	36 (72%)
Centrilobular, necrosis	4 (8%)	9 (18%)	5 (10%)	4 (8%)
Kupffer cell, pigmentation	23 (46%)	30 (60%)	34 (68%)	42 (84%)
Mesentery	(8)	(6)	(15)	(8)
Fat, necrosis	8 (100%)	6 (100%)	11 (73%)	8 (100%)
Oral mucosa	(3)	(1)	(1)	
Pharyngeal, hyperplasia, squamous			1 (100%)	
Pancreas	(50)	(50)	(50)	(50)
Atrophy	25 (50%)	25 (50%)	26 (52%)	22 (44%)
Basophilic focus	3 (6%)	2 (4%)	5 (10%)	2 (4%)
Hyperplasia	3 (6%)	5 (10%)	2 (4%)	2 (4%)

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Alimentary System (continued)				
Salivary glands	(50)	(50)	(50)	(50)
Artery, mineralization		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Mineralization		2 (4%)		
Necrosis	1 (2%)			
Ulcer	7 (14%)	9 (18%)	3 (6%)	3 (6%)
Epithelium, hyperplasia	5 (10%)	8 (16%)	4 (8%)	4 (8%)
Stomach, glandular	(49)	(49)	(50)	(50)
Inflammation, acute		1 (2%)		
Mineralization	1 (2%)	3 (6%)	2 (4%)	4 (8%)
Necrosis	4 (8%)	8 (16%)	4 (8%)	10 (20%)
Tooth	(3)	(1)		
Inflammation, chronic active	3 (100%)	1 (100%)		
Malformation	1 (33%)			
Cardiovascular System				
Blood vessel		(2)		
Aorta, mineralization		2 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	42 (84%)	44 (88%)	39 (78%)	41 (82%)
Artery, mineralization		2 (4%)		
Atrium, thrombosis	1 (2%)	6 (12%)	4 (8%)	3 (6%)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Atrophy	1 (2%)		3 (6%)	2 (4%)
Hyperplasia	23 (46%)	27 (54%)	25 (51%)	30 (60%)
Hypertrophy	7 (14%)	7 (14%)	8 (16%)	4 (8%)
Necrosis	1 (2%)		1 (2%)	1 (2%)
Vacuolization cytoplasmic	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	24 (48%)	22 (44%)	31 (63%)	27 (54%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia		2 (4%)	4 (8%)	1 (2%)
Parathyroid gland	(47)	(46)	(47)	(44)
Hyperplasia	4 (9%)	7 (15%)	2 (4%)	3 (7%)
Pituitary gland	(49)	(49)	(48)	(47)
Cyst	1 (2%)			
Mineralization		1 (2%)		
Pars distalis, hyperplasia	16 (33%)	12 (24%)	16 (33%)	14 (30%)
Pars intermedia, hyperplasia			1 (2%)	1 (2%)
Thyroid gland	(50)	(46)	(48)	(48)
C-cell, hyperplasia	23 (46%)	31 (67%)	32 (67%)	17 (35%)
Follicular cell, hyperplasia			1 (2%)	1 (2%)
General Body System				
None				

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)	1 (2%)		1 (2%)
Preputial gland	(46)	(47)	(50)	(43)
Hyperplasia		3 (6%)		4 (9%)
Inflammation, chronic active	1 (2%)	5 (11%)	2 (4%)	1 (2%)
Prostate	(49)	(49)	(50)	(50)
Hyperplasia	6 (12%)	9 (18%)	4 (8%)	8 (16%)
Inflammation, chronic active	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Seminal vesicle	(47)	(44)	(46)	(48)
Hyperplasia				1 (2%)
Mineralization		2 (5%)		
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Artery, inflammation, chronic active		1 (2%)		
Interstitial cell, hyperplasia	5 (10%)	2 (4%)	5 (10%)	8 (16%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia	5 (10%)	4 (8%)	4 (8%)	6 (12%)
Necrosis			1 (2%)	
Lymph node, mandibular	(44)	(47)	(47)	(46)
Infiltration cellular, plasma cell		1 (2%)		
Lymph node, mediastinal	(44)	(44)	(45)	(44)
Infiltration cellular, plasma cell		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Fibrosis	11 (22%)	14 (28%)	19 (38%)	20 (40%)
Hematopoietic cell proliferation	8 (16%)	8 (16%)	6 (12%)	5 (10%)
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, focal, lymphoid		1 (2%)		
Necrosis	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Pigmentation, hemosiderin	45 (90%)	45 (90%)	40 (80%)	44 (88%)
Integumentary System				
Mammary gland	(44)	(40)	(44)	(45)
Galactocele			1 (2%)	1 (2%)
Hyperplasia			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)	
Hyperkeratosis	1 (2%)	1 (2%)	3 (6%)	
Inflammation, chronic active	2 (4%)	1 (2%)	4 (8%)	
Subcutaneous tissue, thrombosis	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	3 (6%)		
Hyperostosis			2 (4%)	2 (4%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression				1 (2%)
Hemorrhage		1 (2%)		
Hydrocephalus				1 (2%)
Mineralization		1 (2%)		1 (2%)
Thrombosis			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Infiltration cellular, histiocyte	1 (2%)	1 (2%)	2 (4%)	
Inflammation, chronic active		1 (2%)	3 (6%)	3 (6%)
Inflammation, suppurative			1 (2%)	
Mineralization		2 (4%)		
Necrosis	1 (2%)			
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	5 (10%)	13 (26%)	6 (12%)	14 (28%)
Artery, infiltration cellular, histiocyte	2 (4%)			
Artery, mediastinum, mineralization		2 (4%)		
Mediastinum, inflammation, chronic	1 (2%)			
Nose	(48)	(49)	(49)	(50)
Inflammation, suppurative	7 (15%)	7 (14%)	10 (20%)	5 (10%)
Thrombosis	7 (15%)	13 (27%)	11 (22%)	10 (20%)
Olfactory epithelium, degeneration, hyaline	13 (27%)	21 (43%)	23 (47%)	40 (80%)
Olfactory epithelium, metaplasia	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Respiratory epithelium, hyperplasia	4 (8%)	4 (8%)	6 (12%)	1 (2%)
Respiratory epithelium, metaplasia, squamous			1 (2%)	
Trachea	(50)	(49)	(50)	(48)
Infiltration cellular, polymorphonuclear		1 (2%)		
Special Senses System				
Eye	(2)		(2)	(1)
Cataract	2 (100%)		2 (100%)	1 (100%)
Retina, atrophy	2 (100%)		2 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Hydronephrosis		1 (2%)		
Infarct	1 (2%)	2 (4%)	1 (2%)	6 (12%)
Mineralization		2 (4%)		
Nephropathy	48 (96%)	50 (100%)	49 (98%)	50 (100%)
Cortex, cyst		1 (2%)	1 (2%)	
Pelvis, inflammation, acute	1 (2%)			
Renal tubule, hyperplasia	3 (6%)	1 (2%)		1 (2%)
Renal tubule, necrosis		2 (4%)		

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

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	21	23	26
Natural deaths	3	2	4	3
Survivors				
Terminal sacrifice	29	27	23	21
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Intestine large, rectum	(44)	(47)	(48)	(47)
Intestine large, cecum	(47)	(49)	(48)	(48)
Intestine small, duodenum	(49)	(49)	(49)	(48)
Histiocytic sarcoma			1 (2%)	
Intestine small, jejunum	(47)	(49)	(47)	(48)
Histiocytic sarcoma			1 (2%)	
Intestine small, ileum	(47)	(50)	(47)	(47)
Histiocytic sarcoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Mesentery	(12)	(9)	(8)	(3)
Hemangioma			1 (13%)	
Sex cord stromal tumor, malignant, metastatic, ovary	1 (8%)			
Pancreas	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Salivary glands	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Stomach, glandular	(50)	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		2 (4%)	
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Bilateral, carcinoma			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(49)	(49)
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	3 (6%)	4 (8%)	1 (2%)	6 (12%)
Bilateral, pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	1 (2%)			1 (2%)
Carcinoma		1 (2%)		
Pituitary gland	(50)	(50)	(49)	(49)
Histiocytic sarcoma			1 (2%)	
Pars distalis, adenoma	33 (66%)	32 (64%)	30 (61%)	20 (41%)
Thyroid gland	(50)	(48)	(49)	(50)
Histiocytic sarcoma			1 (2%)	
C-cell, adenoma	6 (12%)	2 (4%)	5 (10%)	5 (10%)
C-cell, carcinoma			2 (4%)	2 (4%)
Follicular cell, adenoma	1 (2%)			1 (2%)
Follicular cell, carcinoma	1 (2%)			1 (2%)
General Body System				
Peritoneum				(1)
Genital System				
Clitoral gland	(46)	(45)	(44)	(48)
Adenoma	6 (13%)	3 (7%)	4 (9%)	4 (8%)
Carcinoma	3 (7%)	1 (2%)	3 (7%)	2 (4%)
Histiocytic sarcoma			1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign			1 (2%)	
Granulosa-theca tumor malignant				1 (2%)
Histiocytic sarcoma			1 (2%)	
Sex cord stromal tumor, malignant	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Deciduoma benign	1 (2%)			
Deciduoma NOS	1 (2%)			
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Polyp stromal	6 (12%)	3 (6%)	5 (10%)	2 (4%)
Polyp stromal, multiple			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(5)	(3)	(6)	(2)
Histiocytic sarcoma			1 (17%)	
Renal, histiocytic sarcoma			1 (17%)	
Renal, osteosarcoma, metastatic, bone	1 (20%)			
Lymph node, bronchial	(33)	(36)	(34)	(26)
Histiocytic sarcoma			1 (3%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(43)	(46)	(46)
Histiocytic sarcoma			1 (2%)	
Lymph node, mesenteric	(48)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Lymph node, mediastinal	(38)	(43)	(39)	(28)
Histiocytic sarcoma			1 (3%)	
Spleen	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Thymus	(48)	(47)	(49)	(44)
Histiocytic sarcoma			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(49)
Carcinoma	3 (6%)	4 (8%)	4 (8%)	3 (6%)
Fibroadenoma	19 (38%)	16 (32%)	10 (20%)	12 (24%)
Fibroadenoma, multiple	4 (8%)	8 (16%)	10 (20%)	3 (6%)
Histiocytic sarcoma			1 (2%)	
Skin	(49)	(50)	(50)	(50)
Basal cell carcinoma	1 (2%)	1 (2%)		
Keratoacanthoma	2 (4%)			
Squamous cell papilloma				2 (4%)
Subcutaneous tissue, fibroma		1 (2%)		1 (2%)
Subcutaneous tissue, lipoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma				1 (2%)
Osteosarcoma, multiple	1 (2%)			
Skeletal muscle			(1)	(2)
Hemangioma			1 (100%)	
Sarcoma				1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant		1 (2%)		
Glioma malignant			1 (2%)	
Histiocytic sarcoma			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lung	(50)	(50)	(50)	(49)
Carcinoma, metastatic, mammary gland				1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)	1 (2%)
Chordoma, metastatic, bone				1 (2%)
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Sarcoma, metastatic, skeletal muscle				1 (2%)
Nose	(50)	(48)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Special Senses System				
Zymbal's gland		(1)		(1)
Carcinoma		1 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Sex cord stromal tumor, malignant, metastatic, ovary	1 (2%)			
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	18 (36%)	21 (42%)	23 (46%)	24 (48%)
Mesothelioma malignant				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	48	50	48
Total primary neoplasms	112	99	108	98
Total animals with benign neoplasms	42	43	40	37
Total benign neoplasms	83	69	72	58
Total animals with malignant neoplasms	26	26	30	32
Total malignant neoplasms	28	30	36	40
Total animals with metastatic neoplasms	2		1	4
Total metastatic neoplasms	7		1	4
Total animals with uncertain neoplasms-benign or malignant	1			
Total uncertain neoplasms	1			

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

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

Number of Days on Study	4 0 0	5 0 8	5 3 3	5 5 4	5 5 8	5 7 5	5 9 4	6 1 7	6 1 7	6 3 8	6 4 8	6 5 2	6 5 4	6 8 7	6 8 8	7 0 8	7 1 0	7 1 8	7 1 8	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 3 3	1 3 8	1 1 3	1 0 7	1 4 9	1 2 8	1 3 2	1 1 6	1 2 5	1 4 7	1 4 8	1 4 0	1 4 2	1 1 2	1 3 7	1 3 5	1 2 9	1 0 6	1 1 5	1 4 1	1 3 4	1 0 9	1 1 1	1 1 4	1 1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	I	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+				+			+						+	+		+
Sex cord stromal tumor, malignant, metastatic, ovary																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Osteosarcoma, metastatic, bone			X																						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone			X																						
Pheochromocytoma benign				X																	X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X		X	X		X			X	X	X	X	X	X		X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X		X			X					
Follicular cell, adenoma																									
Follicular cell, carcinoma																									
General Body System																									
None																									

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

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 8	1 2 1	1 3 1	1 3 9	1 4 4	1 5 0	1 0 1	1 0 2	1 0 3	1 0 4	1 0 5	1 0 8	1 1 0	1 1 9	1 2 0	1 2 2	1 2 3	1 2 4	1 2 6	1 2 7	1 3 0	1 3 6	1 4 3	1 4 5	1 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+			+						+						+	+			+				12
Sex cord stromal tumor, malignant, metastatic, ovary																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Osteosarcoma, metastatic, bone																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma benign																							X			3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X			X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X		X							X							6
Follicular cell, adenoma																							X			1
Follicular cell, carcinoma																									X	1
General Body System																										
None																										

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

Number of Days on Study	4 0 0	5 0 8	5 3 3	5 5 4	5 5 8	5 7 5	5 9 4	6 1 7	6 1 7	6 3 8	6 4 8	6 5 2	6 5 4	6 8 7	6 8 8	7 0 8	7 1 0	7 1 8	7 1 8	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 1 3 3	1 3 8	1 1 3	1 0 7	1 4 9	1 2 8	1 3 2	1 1 6	1 2 5	1 4 7	1 4 8	1 4 0	1 4 2	1 1 2	1 3 7	1 3 5	1 2 9	1 0 6	1 1 5	1 4 1	1 3 4	1 0 9	1 1 1	1 1 4	1 1 7
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma															X										
Carcinoma																					X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sex cord stromal tumor, malignant																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign																									
Deciduoma NOS																				X					
Polyp stromal				X																			X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+						+	+								+							
Renal, osteosarcoma, metastatic, bone			X																						
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M	M	M	+	+	+	M	M	+	M
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Fibroadenoma		X			X	X		X				X	X	X		X			X						
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, multiple			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 8	1 2 1	1 3 1	1 3 9	1 4 4	1 5 0	1 0 1	1 0 2	1 0 3	1 0 4	1 0 5	1 0 8	1 1 0	1 1 9	1 2 0	1 2 2	1 2 3	1 2 4	1 2 6	1 2 7	1 3 0	1 3 6	1 4 3	1 4 5	1 4 6	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Adenoma					X								X					X		X			X			6
Carcinoma	X														X											3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sex cord stromal tumor, malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma benign																				X						1
Deciduoma NOS																										1
Polyp stromal	X									X					X					X					6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										5
Renal, osteosarcoma, metastatic, bone																										1
Lymph node, bronchial	+	+	+	M	+	+	M	M	M	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	33
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	+	+	+	M	M	M	M	+	+	+	+	M	+	+	+	M	+	M	+	+	+	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X		X						3
Fibroadenoma	X							X	X							X	X		X	X	X		X	X		19
Fibroadenoma, multiple		X					X						X													4
Skin	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Basal cell carcinoma				X																						1
Keratoacanthoma																									X	2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, multiple																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	0	0	3	5	5	7	9	1	1	3	4	5	5	8	8	0	1	1	1	1	2	3	3	3	3	
	0	8	3	4	8	5	4	7	7	8	8	2	4	7	8	8	0	8	8	2	2	0	0	0	0	
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	3	3	1	0	4	2	3	1	2	4	4	4	4	1	3	3	2	0	1	4	3	0	1	1	1	
	3	8	3	7	9	8	2	6	5	7	8	0	2	2	7	5	9	6	5	1	4	9	1	4	7	
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Osteosarcoma, metastatic, bone			X																							
Sex cord stromal tumor, malignant, metastatic, ovary																X										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X	X		X			X		X	X				X	X			X								

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

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 8	1 2 1	1 3 1	1 3 9	1 4 4	1 5 0	1 0 1	1 0 2	1 0 3	1 0 4	1 0 5	1 0 8	1 1 0	1 1 9	1 2 0	1 2 2	1 2 3	1 2 4	1 2 6	1 2 7	1 3 0	1 3 6	1 4 3	1 4 5	1 4 6	Total Tissues/ Tumors
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Sex cord stromal tumor, malignant, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X				X	X							X			X	X	X	X	X		18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 4	3 1 6	3 1 7	3 2 4	3 2 8	3 3 3	3 4 1	3 4 2	3 4 4	3 4 6	3 0 1	3 0 2	3 0 4	3 0 6	3 0 8	3 0 9	3 1 3	3 2 0	3 2 2	3 3 2	3 3 5	3 3 6	3 3 7	3 3 9	3 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+			+								+														9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X													4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X			X		X	X	X		X		X	X	X		X	X		X	X	X	X	X	X	32
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	M	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma				X																						3
Carcinoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X						X												X				3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																									+	3
Lymph node, bronchial	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	36
Lymph node, mandibular	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	4 9 5	5 4 4	5 5 3	5 6 1	5 6 4	5 8 4	6 0 6	6 1 0	6 1 7	6 3 8	6 5 2	6 5 2	6 5 5	6 6 6	6 6 7	6 8 7	6 9 1	7 0 1	7 0 7	7 0 8	7 2 2	7 2 2	7 2 9	7 3 0	7 3 0
Carcass ID Number	3 2 3	3 2 1	3 4 5	3 2 6	3 0 3	3 4 3	3 1 9	3 4 0	3 3 0	3 3 8	3 0 7	3 1 5	3 3 4	3 5 0	3 4 9	3 3 1	3 1 8	3 2 7	3 2 5	3 1 0	3 1 1	3 4 7	3 2 9	3 0 5	3 1 2
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X						X	X						X					
Fibroadenoma						X		X							X	X	X						X	X	X
Fibroadenoma, multiple												X								X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant											X														
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																				+	+				
Zymbal's gland																	+								
Carcinoma																	X								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X	X		X				X	X				X		X	X	X	X		X		X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 31.2 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 4	3 1 6	3 1 7	3 2 4	3 2 8	3 3 3	3 4 1	3 4 2	3 4 4	3 4 6	3 0 1	3 0 2	3 0 4	3 0 6	3 0 8	3 0 9	3 1 3	3 2 0	3 2 2	3 3 2	3 3 5	3 3 6	3 3 7	3 3 9	3 4 8	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										4
Fibroadenoma	X					X			X				X	X			X					X			X	16
Fibroadenoma, multiple			X					X							X	X							X			8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																		X								1
Subcutaneous tissue, fibroma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+	+						+				+							+		7
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X		X										X			X	X			X	21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 2 2	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 3	5 3 3	5 0 4	5 0 5	5 0 6	5 1 1	5 1 6	5 1 8	5 2 0	5 2 2	5 2 7	5 3 6	5 4 9	5 0 9	5 2 1	5 2 4	5 2 6	5 2 9	5 3 0	5 3 1	5 3 5	5 3 7	5 3 8	5 4 2	5 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery															+					+	+					8
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																X			2
Histiocytic sarcoma																										1
Bilateral, carcinoma																						X				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Pheochromocytoma benign										X																1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Pars distalis, adenoma	X	X	X	X		X		X	X	X	X	X		X			X	X	X	X		X		X	X	30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
C-cell, adenoma							X								X		X									5
C-cell, carcinoma														X												2
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	2 4 7	3 9 0	4 6 2	4 6 2	4 9 6	5 2 9	5 4 4	5 4 4	5 7 4	5 8 3	5 8 6	5 8 9	6 1 9	6 3 3	6 4 8	6 4 9	6 5 6	6 6 6	6 8 8	6 8 8	6 9 1	6 9 4	6 9 9	7 0 5	7 0 8
Carcass ID Number	5 1 4	5 1 2	5 1 0	5 1 3	5 2 5	5 3 4	5 0 7	5 0 8	5 1 9	5 0 2	5 3 2	5 4 6	5 2 3	5 0 3	5 4 8	5 2 8	5 4 0	5 4 4	5 0 1	5 4 1	5 1 5	5 4 5	5 4 7	5 1 7	5 3 9
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Adenoma																									
Carcinoma										X							X								
Histiocytic sarcoma						X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Histiocytic sarcoma						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Histiocytic sarcoma						X																			
Polyp stromal																								X	
Polyp stromal, multiple																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+				+	+			+		+						+			
Histiocytic sarcoma						X																			
Renal, histiocytic sarcoma						X																			
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+
Histiocytic sarcoma						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X								X													X
Fibroadenoma			X												X				X		X		X		
Fibroadenoma, multiple												X								X					
Histiocytic sarcoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Hemangioma																				X					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant	X																								
Histiocytic sarcoma						X																			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 2 2	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 3	5 3 3	5 0 4	5 0 5	5 0 6	5 1 1	5 1 6	5 1 8	5 2 0	5 2 2	5 2 7	5 3 6	5 4 9	5 0 9	5 2 1	5 2 4	5 2 6	5 2 9	5 3 0	5 3 1	5 3 5	5 3 7	5 3 8	5 4 2	5 5 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	44
Adenoma	X									X					X	X										4
Carcinoma													X													3
Histiocytic sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign									X																	1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Polyp stromal			X	X											X			X								5
Polyp stromal, multiple																			X							1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										6
Histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, bronchial	M	M	M	+	M	+	M	M	M	+	M	+	+	+	M	+	M	M	+	M	+	+	+	+	+	34
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	M	M	M	M	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	+	+	M	39
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X												4
Fibroadenoma													X				X		X	X			X			10
Fibroadenoma, multiple	X		X			X	X		X	X					X			X								10
Histiocytic sarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangioma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Histiocytic sarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	2 4 7	3 9 0	4 6 2	4 6 2	4 9 6	5 2 9	5 4 4	5 4 4	5 7 4	5 8 3	5 8 6	5 8 9	6 1 9	6 3 3	6 4 8	6 4 9	6 5 6	6 6 6	6 8 8	6 8 8	6 9 1	6 9 4	6 9 9	7 0 5	7 0 8
Carcass ID Number	5 1 4	5 1 2	5 1 0	5 1 3	5 2 5	5 3 4	5 0 7	5 0 8	5 1 9	5 0 2	5 3 2	5 4 6	5 2 3	5 0 3	5 4 8	5 2 8	5 4 0	5 4 4	5 0 1	5 4 1	5 1 5	5 4 5	5 4 7	5 1 7	5 3 9
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Histiocytic sarcoma						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	A				+						+														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Leukemia mononuclear		X		X			X		X		X			X	X	X	X	X	X	X		X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 2 2	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 4 3	5 3 3	5 0 4	5 0 5	5 0 6	5 1 1	5 1 6	5 1 8	5 2 0	5 2 2	5 2 7	5 3 6	5 4 9	5 0 9	5 2 1	5 2 4	5 2 6	5 2 9	5 3 0	5 3 1	5 3 5	5 3 7	5 3 8	5 4 2	5 5 0	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland														X												1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye							+																			3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X		X	X		X	X			X		X								X	X				23

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	4 6 2	4 7 2	5 3 3	5 4 1	5 7 1	6 1 0	6 1 0	6 1 2	6 1 7	6 2 4	6 3 8	6 4 6	6 5 2	6 6 2	6 6 3	6 6 3	6 6 6	6 6 7	6 8 5	6 8 9	6 8 9	6 8 9	6 9 4	6 9 4	6 9 5
Carcass ID Number	7 4 6	7 4 5	7 1 1	7 4 8	7 4 2	7 0 9	7 3 2	7 2 0	7 3 8	7 0 4	7 2 6	7 1 4	7 1 2	7 2 7	7 1 7	7 1 8	7 2 8	7 3 6	7 2 4	7 2 5	7 3 7	7 4 9	7 2 2	7 2 3	7 1 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	I	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery								+															+		
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pheochromocytoma malignant								X																	
Pheochromocytoma benign											X	X			X	X								X	
Bilateral, pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	A	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X					X			X	X				X		X			X			X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma								X										X						X	
C-cell, carcinoma																									
Follicular cell, adenoma																									
Follicular cell, carcinoma														X											
General Body System																									
Peritoneum																			+						
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma															X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X	
Polyp stromal														X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 0 1	7 0 5	7 0 5	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 4 4	7 4 0	7 4 1	7 0 6	7 0 5	7 2 1	7 2 9	7 3 3	7 3 5	7 4 3	7 4 7	7 0 1	7 0 2	7 0 3	7 0 7	7 0 8	7 1 0	7 1 3	7 1 5	7 1 9	7 3 0	7 3 1	7 3 4	7 3 9	7 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																		+								3
Oral mucosa																							+			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																										1
Pheochromocytoma benign																					X					6
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X	X		X		X	X	X			X	X					X		X				20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma														X											X	5
C-cell, carcinoma																								X	X	2
Follicular cell, adenoma						X																				1
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma									X									X		X						4
Carcinoma										X																2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Polyp stromal																			X							2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	4 6 2	4 7 2	5 3 3	5 4 1	5 7 1	6 1 0	6 1 0	6 1 2	6 1 7	6 2 4	6 3 8	6 4 6	6 5 2	6 6 2	6 6 3	6 6 3	6 6 6	6 6 7	6 8 5	6 8 9	6 8 9	6 8 9	6 9 4	6 9 4	6 9 5
Carcass ID Number	7 4 6	7 4 5	7 1 1	7 4 8	7 4 2	7 0 9	7 3 2	7 2 0	7 3 8	7 0 4	7 2 6	7 1 4	7 1 2	7 2 7	7 1 7	7 1 8	7 2 8	7 3 6	7 2 4	7 2 5	7 3 7	7 4 9	7 2 2	7 2 3	7 1 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+													
Lymph node, bronchial	M	+	+	+	+	+	M	+	M	+	+	M	+	M	M	+	+	M	M	M	M	M	+	M	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	M	M	+	M	+	M	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Fibroadenoma	X					X	X			X							X	X				X			
Fibroadenoma, multiple													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Skeletal muscle												+		+											
Sarcoma												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Carcinoma, metastatic, thyroid gland																									
Chordoma, metastatic, bone																									
Sarcoma, metastatic, skeletal muscle												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+																				
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X	X	X	X		X	X	X			X	X			X	X	X	X	X	
Mesothelioma malignant																			X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 0 1	7 0 5	7 0 5	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 4 4	7 4 0	7 4 1	7 0 6	7 0 5	7 2 1	7 2 9	7 3 3	7 3 5	7 4 3	7 4 7	7 0 1	7 0 2	7 0 3	7 0 7	7 0 8	7 1 0	7 1 3	7 1 5	7 1 9	7 3 0	7 3 1	7 3 4	7 3 9	7 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																									2
Lymph node, bronchial	+	M	+	+	+	+	M	M	M	M	M	M	+	+	+	+	+	+	M	M	M	M	+	M	+	26
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	M	M	M	M	M	M	+	+	+	+	+	+	+	M	M	M	M	M	+	M	28
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	M	44
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma			X												X											3
Fibroadenoma		X							X			X					X							X	12
Fibroadenoma, multiple				X																X						3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						2
Subcutaneous tissue, fibroma						X																				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma															X											1
Skeletal muscle																										2
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	49
Carcinoma, metastatic, mammary gland			X																							1
Carcinoma, metastatic, thyroid gland																									X	1
Chordoma, metastatic, bone															X											1
Sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland												+														1
Carcinoma												X														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X				X					X							X	X			X		24
Mesothelioma malignant																										1

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	4/50 (8%)	1/49 (2%)	7/49 (14%)
Adjusted rate[b]	6.9%	9.2%	2.6%	16.7%
Terminal rate[c]	1/29 (3%)	1/27 (4%)	1/22 (5%)	1/21 (5%)
First incidence (days)	554	584	730 (T)	638
Poly-3 test[d]	P=0.090	P=0.499	P=0.353N	P=0.138
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/49 (2%)	8/49 (16%)
Adjusted rate	6.9%	9.2%	2.6%	18.9%
Terminal rate	1/29 (3%)	1/27 (4%)	1/22 (5%)	1/21 (5%)
First incidence (days)	554	584	730 (T)	612
Poly-3 test	P=0.044	P=0.499	P=0.353N	P=0.086
Clitoral Gland: Adenoma				
Overall rate	6/46 (13%)	3/45 (7%)	4/44 (9%)	4/48 (8%)
Adjusted rate	14.9%	7.8%	11.8%	10.1%
Terminal rate	5/27 (19%)	1/23 (4%)	3/20 (15%)	3/20 (15%)
First incidence (days)	688	722	722	646
Poly-3 test	P=0.385N	P=0.262N	P=0.479N	P=0.374N
Clitoral Gland: Carcinoma				
Overall rate	3/46 (7%)	1/45 (2%)	3/44 (7%)	2/48 (4%)
Adjusted rate	7.5%	2.6%	8.7%	5.0%
Terminal rate	2/27 (7%)	1/23 (4%)	1/20 (5%)	1/20 (5%)
First incidence (days)	722	730 (T)	583	663
Poly-3 test	P=0.523N	P=0.320N	P=0.594	P=0.503N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	9/46 (20%)	3/45 (7%)	7/44 (16%)	6/48 (13%)
Adjusted rate	22.4%	7.8%	20.2%	15.0%
Terminal rate	7/27 (26%)	1/23 (4%)	4/20 (20%)	4/20 (20%)
First incidence (days)	688	722	583	646
Poly-3 test	P=0.395N	P=0.066N	P=0.521N	P=0.285N
Mammary Gland: Fibroadenoma				
Overall rate	23/50 (46%)	24/50 (48%)	20/50 (40%)	15/50 (30%)
Adjusted rate	49.9%	53.5%	48.2%	33.9%
Terminal rate	14/29 (48%)	15/27 (56%)	12/23 (52%)	5/21 (24%)
First incidence (days)	508	584	462	462
Poly-3 test	P=0.043N	P=0.445	P=0.522N	P=0.088N
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted rate	6.9%	9.1%	9.8%	7.2%
Terminal rate	2/29 (7%)	0/27 (0%)	1/23 (4%)	1/21 (5%)
First incidence (days)	638	606	462	663
Poly-3 test	P=0.571N	P=0.507	P=0.464	P=0.642

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	25/50 (50%)	27/50 (54%)	23/50 (46%)	18/50 (36%)
Adjusted rate	53.8%	58.9%	54.3%	40.4%
Terminal rate	15/29 (52%)	15/27 (56%)	13/23 (57%)	6/21 (29%)
First incidence (days)	508	584	462	462
Poly-3 test	P=0.070N	P=0.386	P=0.568	P=0.137N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	33/50 (66%)	32/50 (64%)	30/49 (61%)	20/49 (41%)
Adjusted rate	72.8%	69.1%	69.5%	45.6%
Terminal rate	22/29 (76%)	19/27 (70%)	16/23 (70%)	9/21 (43%)
First incidence (days)	575	584	496	462
Poly-3 test	P=0.002N	P=0.430N	P=0.452N	P=0.005N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	6.9%	2.3%	0.0%	4.8%
Terminal rate	2/29 (7%)	1/27 (4%)	0/23 (0%)	0/21 (0%)
First incidence (days)	710	730 (T)	—[e]	695
Poly-3 test	P=0.457N	P=0.307N	P=0.135N	P=0.520N
Thyroid Gland (C-cell): Adenoma				
Overall rate	6/50 (12%)	2/48 (4%)	5/49 (10%)	5/50 (10%)
Adjusted rate	13.8%	4.8%	12.6%	11.9%
Terminal rate	3/29 (10%)	0/27 (0%)	3/23 (13%)	2/21 (10%)
First incidence (days)	688	701	694	612
Poly-3 test	P=0.514	P=0.145N	P=0.564N	P=0.523N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	2/48 (4%)	7/49 (14%)	6/50 (12%)
Adjusted rate	13.8%	4.8%	17.5%	14.3%
Terminal rate	3/29 (10%)	0/27 (0%)	4/23 (17%)	3/21 (14%)
First incidence (days)	688	701	649	612
Poly-3 test	P=0.341	P=0.145N	P=0.435	P=0.598
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	3/50 (6%)	6/50 (12%)	2/50 (4%)
Adjusted rate	13.7%	7.0%	15.2%	4.8%
Terminal rate	5/29 (17%)	3/27 (11%)	5/23 (22%)	1/21 (5%)
First incidence (days)	554	730 (T)	705	662
Poly-3 test	P=0.182N	P=0.249N	P=0.549	P=0.149N
All Organs: Mononuclear Cell Leukemia				
Overall rate	18/50 (36%)	21/50 (42%)	23/50 (46%)	24/50 (48%)
Adjusted rate	38.5%	44.3%	51.5%	51.2%
Terminal rate	9/29 (31%)	7/27 (26%)	8/23 (35%)	5/21 (24%)
First incidence (days)	400	495	390	533
Poly-3 test	P=0.117	P=0.358	P=0.145	P=0.149

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

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	43/50 (86%)	40/50 (80%)	37/50 (74%)
Adjusted rate	88.1%	91.3%	88.9%	78.9%
Terminal rate	25/29 (86%)	25/27 (93%)	21/23 (91%)	17/21 (81%)
First incidence (days)	508	584	462	462
Poly-3 test	P=0.059N	P=0.418	P=0.588	P=0.163N
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	26/50 (52%)	30/50 (60%)	32/50 (64%)
Adjusted rate	54.7%	54.1%	63.2%	67.1%
Terminal rate	14/29 (48%)	9/27 (33%)	9/23 (39%)	9/21 (43%)
First incidence (days)	400	495	247	533
Poly-3 test	P=0.085	P=0.555N	P=0.261	P=0.148
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	48/50 (96%)	50/50 (100%)	48/50 (96%)
Adjusted rate	94.0%	96.0%	100.0%	97.4%
Terminal rate	26/29 (90%)	25/27 (93%)	23/23 (100%)	20/21 (95%)
First incidence (days)	400	495	247	462
Poly-3 test	P=0.212	P=0.500	P=0.119	P=0.363

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Adrenal Gland Pheochromocytoma in Chamber Control Female F344/N Rats[a]

	Incidence in Controls			
	Benign	Complex	Malignant	Benign, Complex, or Malignant[b]
Historical Incidence at Battelle Pacific Northwest Laboratories				
Acetonitrile	1/48	0/48	0/48	1/48
Chloroprene	3/49	0/49	0/49	3/49
Cobalt sulfate heptahydrate	2/48	0/48	0/48	2/48
Furfuryl alcohol	4/50	0/50	1/50	5/50
Hexachlorocyclopentadiene	6/47	0/47	0/47	6/47
Isobutene	3/50	1/50	0/50	4/50
Isobutyraldehyde	1/49	0/49	0/49	1/49
Isoprene	1/50	0/50	1/50	2/50
Molybdenum trioxide	5/49	1/49	0/49	6/49
Nitromethane	1/49	1/49	0/49	2/49
Ozone	6/50	0/50	0/50	6/50
Tetrafluoroethane	4/50	0/50	0/50	4/50
Tetrahydrofuran	0/50	0/50	2/50	2/50
Overall Historical Incidence				
Total (%)	47/889 (5.3%)	5/889 (0.6%)	5/889 (0.6%)	57/889 (6.4%)
Mean ± standard deviation	5.3% ± 3.9%	0.6% ± 1.2%	0.6% ± 1.1%	6.4% ± 3.5%
Range	0%-13%	0%-4%	0%-4%	2%-13%

[a] Data as of 12 November 1997
[b] Includes data for unspecified pheochromocytomas

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	21	23	26
Natural deaths	3	2	4	3
Survivors				
Terminal sacrifice	29	27	23	21
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(50)	(50)	(49)
Necrosis				1 (2%)
Parasite metazoan	4 (8%)	5 (10%)	2 (4%)	3 (6%)
Intestine large, rectum	(44)	(47)	(48)	(47)
Parasite metazoan	1 (2%)	4 (9%)	3 (6%)	4 (9%)
Intestine large, cecum	(47)	(49)	(48)	(48)
Inflammation, chronic				1 (2%)
Parasite metazoan	8 (17%)	6 (12%)	4 (8%)	5 (10%)
Intestine small, ileum	(47)	(50)	(47)	(47)
Inflammation, chronic active		1 (2%)		1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)		1 (2%)
Basophilic focus	39 (78%)	41 (82%)	41 (82%)	38 (76%)
Clear cell focus	12 (24%)	8 (16%)	5 (10%)	9 (18%)
Degeneration, cystic				1 (2%)
Eosinophilic focus	13 (26%)	10 (20%)	6 (12%)	5 (10%)
Fatty change	11 (22%)	12 (24%)	12 (24%)	6 (12%)
Hematopoietic cell proliferation	4 (8%)	5 (10%)	1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	6 (12%)	3 (6%)	1 (2%)
Inflammation, granulomatous		1 (2%)		
Mixed cell focus	6 (12%)	2 (4%)	4 (8%)	4 (8%)
Necrosis	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Regeneration	1 (2%)			3 (6%)
Vacuolization cytoplasmic, focal	1 (2%)			
Bile duct, hyperplasia	8 (16%)	8 (16%)	8 (16%)	5 (10%)
Centrilobular, necrosis	2 (4%)	1 (2%)	1 (2%)	5 (10%)
Kupffer cell, pigmentation	15 (30%)	19 (38%)	36 (72%)	47 (94%)
Mesentery	(12)	(9)	(8)	(3)
Artery, inflammation, chronic active			1 (13%)	
Fat, necrosis	12 (100%)	9 (100%)	6 (75%)	3 (100%)
Oral mucosa				(1)
Pharyngeal, hyperplasia, squamous				1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	17 (34%)	15 (30%)	13 (26%)	13 (26%)
Basophilic focus	2 (4%)	5 (10%)	4 (8%)	
Hyperplasia	1 (2%)	1 (2%)		
Salivary glands	(50)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)		1 (2%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Ulcer	2 (4%)	4 (8%)	7 (14%)	3 (6%)
Epithelium, hyperplasia	3 (6%)	5 (10%)	6 (12%)	2 (4%)
Stomach, glandular	(50)	(50)	(49)	(50)
Mineralization	3 (6%)	3 (6%)	2 (4%)	8 (16%)
Necrosis	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	34 (68%)	31 (62%)	34 (68%)	30 (60%)
Atrium, thrombosis	1 (2%)	2 (4%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule		1 (2%)		
Atrophy		1 (2%)	1 (2%)	
Degeneration, cystic		1 (2%)		3 (6%)
Hyperplasia	28 (56%)	24 (48%)	19 (38%)	20 (40%)
Hypertrophy	18 (36%)	11 (22%)	9 (18%)	7 (14%)
Necrosis		3 (6%)	4 (8%)	3 (6%)
Vacuolization cytoplasmic	7 (14%)	9 (18%)	1 (2%)	5 (10%)
Adrenal medulla	(50)	(50)	(49)	(49)
Hyperplasia	11 (22%)	11 (22%)	8 (16%)	17 (35%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	2 (4%)			
Parathyroid gland	(46)	(48)	(42)	(43)
Hyperplasia			1 (2%)	
Pituitary gland	(50)	(50)	(49)	(49)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Pars distalis, hyperplasia	15 (30%)	14 (28%)	11 (22%)	23 (47%)
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(50)	(48)	(49)	(50)
C-cell, hyperplasia	37 (74%)	41 (85%)	36 (73%)	29 (58%)
Follicular cell, hyperplasia		1 (2%)	1 (2%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(46)	(45)	(44)	(48)
Hyperplasia	7 (15%)	4 (9%)	2 (5%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Cyst	9 (18%)	7 (14%)	3 (6%)	4 (8%)
Hyperplasia		1 (2%)		
Inflammation, granulomatous	1 (2%)		1 (2%)	
Interstitial cell, hyperplasia			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Prolapse			1 (2%)	
Endometrium, hyperplasia, cystic	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia	5 (10%)	2 (4%)	2 (4%)	6 (12%)
Hyperplasia, histiocytic		2 (4%)	1 (2%)	1 (2%)
Lymph node	(5)	(3)	(6)	(2)
Renal, infiltration cellular, plasma cell			1 (17%)	
Spleen	(50)	(50)	(50)	(50)
Fibrosis	2 (4%)	6 (12%)	7 (14%)	7 (14%)
Hematopoietic cell proliferation	11 (22%)	17 (34%)	6 (12%)	4 (8%)
Hemorrhage	1 (2%)		1 (2%)	
Necrosis		1 (2%)		
Pigmentation, hemosiderin	48 (96%)	48 (96%)	48 (96%)	49 (98%)
Thymus	(48)	(47)	(49)	(44)
Cyst			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(49)
Galactocele		2 (4%)		
Hyperplasia, atypical	1 (2%)			
Skin	(49)	(50)	(50)	(50)
Cyst	1 (2%)			
Hyperkeratosis	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	9 (18%)	10 (20%)	8 (16%)	9 (18%)
Inflammation, chronic	1 (2%)			
Skeletal muscle			(1)	(2)
Hemorrhage				1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hydrocephalus		1 (2%)		
Mineralization		1 (2%)		
Necrosis				1 (2%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Epiglottis, metaplasia, squamous	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Lung	(50)	(50)	(50)	(49)
Foreign body		1 (2%)		
Infiltration cellular, histiocyte		2 (4%)	1 (2%)	
Inflammation, chronic active	11 (22%)	11 (22%)	9 (18%)	13 (27%)
Inflammation, granulomatous		1 (2%)		
Thrombosis				1 (2%)
Alveolar epithelium, hyperplasia	17 (34%)	7 (14%)	8 (16%)	5 (10%)
Artery, infiltration cellular, histiocyte		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Respiratory System (continued)				
Nose	(50)	(48)	(50)	(49)
Inflammation, chronic	3 (6%)		1 (2%)	
Inflammation, suppurative	9 (18%)	8 (17%)	5 (10%)	4 (8%)
Thrombosis	2 (4%)	4 (8%)	6 (12%)	5 (10%)
Olfactory epithelium, degeneration, hyaline	13 (26%)	18 (38%)	28 (56%)	40 (82%)
Olfactory epithelium, metaplasia	3 (6%)	2 (4%)		3 (6%)
Olfactory epithelium, metaplasia, squamous				1 (2%)
Respiratory epithelium, hyperplasia	2 (4%)		2 (4%)	1 (2%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	3 (6%)		1 (2%)
Trachea	(50)	(50)	(50)	(50)
Infiltration cellular, polymorphonuclear		1 (2%)		
Special Senses System				
Eye		(7)	(3)	(1)
Cataract		5 (71%)	2 (67%)	1 (100%)
Degeneration			1 (33%)	
Hemorrhage		1 (14%)		
Retina, atrophy		5 (71%)	1 (33%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct		1 (2%)	2 (4%)	3 (6%)
Inflammation, suppurative		1 (2%)		
Nephropathy	47 (94%)	48 (96%)	43 (86%)	46 (92%)
Papilla, necrosis				1 (2%)
Pelvis, inflammation, acute	1 (2%)			
Renal tubule, hyperplasia	1 (2%)	1 (2%)		
Renal tubule, necrosis				2 (4%)
Urinary bladder	(50)	(50)	(49)	(50)
Inflammation, granulomatous	1 (2%)			

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

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	8	13	10
Natural deaths	4	3	10	14
Survivors				
Terminal sacrifice	39	39	27	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(48)	(48)	(44)	(43)
Intestine small, jejunum	(48)	(47)	(43)	(38)
Histiocytic sarcoma				1 (3%)
Intestine small, ileum	(48)	(47)	(43)	(39)
Carcinoma		1 (2%)		
Liver	(50)	(50)	(49)	(49)
Carcinoma, metastatic, islets, pancreatic				1 (2%)
Hemangiosarcoma		1 (2%)	2 (4%)	4 (8%)
Hepatocellular carcinoma	5 (10%)	8 (16%)	12 (24%)	16 (33%)
Hepatocellular carcinoma, multiple	5 (10%)	3 (6%)	4 (8%)	5 (10%)
Hepatocellular adenoma	13 (26%)	10 (20%)	13 (27%)	14 (29%)
Hepatocellular adenoma, multiple	9 (18%)	8 (16%)	5 (10%)	3 (6%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma				2 (4%)
Mesentery	(5)	(3)	(3)	(1)
Histiocytic sarcoma				1 (100%)
Oral mucosa			(1)	
Squamous cell carcinoma			1 (100%)	
Pancreas	(50)	(50)	(47)	(47)
Hemangioma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Salivary glands	(50)	(50)	(48)	(50)
Stomach, forestomach	(50)	(50)	(49)	(48)
Histiocytic sarcoma				1 (2%)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Stomach, glandular	(50)	(50)	(46)	(47)
Adenoma	1 (2%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma				1 (2%)
Capsule, adenoma	2 (4%)	2 (4%)	2 (4%)	
Adrenal medulla	(49)	(50)	(49)	(49)
Pheochromocytoma malignant		1 (2%)		
Islets, pancreatic	(50)	(50)	(47)	(46)
Adenoma	2 (4%)			
Carcinoma				1 (2%)
Thyroid gland	(50)	(48)	(49)	(50)
Follicular cell, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma				1 (2%)
Leiomyoma				1 (2%)
Prostate	(49)	(49)	(48)	(45)
Seminal vesicle	(50)	(49)	(46)	(46)
Histiocytic sarcoma				1 (2%)
Testes	(50)	(50)	(49)	(50)
Interstitial cell, adenoma				2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)		2 (4%)
Histiocytic sarcoma				1 (2%)
Lymph node	(2)	(1)		(1)
Schwannoma malignant, metastatic, spinal cord	1 (50%)			
Lymph node, bronchial	(38)	(35)	(33)	(35)
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Lymph node, mandibular	(24)	(26)	(32)	(25)
Lymph node, mesenteric	(50)	(50)	(47)	(43)
Histiocytic sarcoma				1 (2%)
Lymph node, mediastinal	(40)	(33)	(40)	(37)
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Histiocytic sarcoma				1 (3%)
Spleen	(50)	(50)	(48)	(49)
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma				1 (2%)
Mast cell tumor NOS		1 (2%)		
Thymus	(43)	(43)	(36)	(37)
Histiocytic sarcoma				1 (3%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Hemangioma			1 (2%)	
Prepuce, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Nervous System				
Brain	(50)	(50)	(49)	(50)
Spinal cord	(2)			
Schwannoma malignant	1 (50%)			
Respiratory System				
Larynx	(50)	(50)	(48)	(49)
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	7 (14%)	8 (16%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		2 (4%)	
Alveolar/bronchiolar carcinoma	5 (10%)	2 (4%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	7 (14%)	5 (10%)	5 (10%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma				1 (2%)
Mediastinum, hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Nose	(50)	(50)	(48)	(48)
Special Senses System				
Harderian gland	(3)	(3)	(2)	(2)
Adenoma	3 (100%)	3 (100%)	2 (100%)	2 (100%)
Urinary System				
Kidney	(50)	(50)	(47)	(50)
Histiocytic sarcoma				1 (2%)
Urinary bladder	(50)	(50)	(46)	(45)
Histiocytic sarcoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			2 (4%)
Lymphoma malignant	1 (2%)	3 (6%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	33	36	41
Total primary neoplasms	62	55	60	69
Total animals with benign neoplasms	30	28	26	28
Total benign neoplasms	42	32	37	33
Total animals with malignant neoplasms	19	16	19	28
Total malignant neoplasms	20	22	23	36
Total animals with metastatic neoplasms	9	5	5	4
Total metastatic neoplasms	12	6	5	4
Total animals with benign or malignant neoplasms of uncertain primary site		1		
Total uncertain neoplasms		1		

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

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

Number of Days on Study	3 7 4	4 5 9	5 5 6	5 6 1	5 6 5	6 1 8	6 2 1	6 4 2	6 6 3	6 6 7	6 6 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 1 4	0 5 0	0 1 8	0 2 2	0 1 0	0 4 0	0 3 3	0 3 9	0 1 5	0 1 7	0 0 2	0 0 5	0 0 6	0 0 7	0 1 2	0 1 9	0 2 4	0 2 5	0 3 1	0 3 2	0 3 5	0 3 6	0 3 8	0 4 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	M	+	M	+	+	+	+	A	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma	X					X	X							X				X							
Hepatocellular carcinoma, multiple				X	X				X	X					X										
Hepatocellular adenoma								X					X		X			X			X			X	
Hepatocellular adenoma, multiple																			X						
Hepatocholangiocarcinoma		X																							
Mesentery															+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X							X							
Parathyroid gland	+	M	+	+	M	+	M	M	+	M	+	+	M	+	+	M	+	+	M	M	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	
Carcass ID Number	0 0 4 3	0 0 4 5	0 0 4 6	0 0 1 1	0 0 1 4	0 0 1 8	0 0 2 9	0 0 3 1	0 1 1 1	0 1 1 3	0 2 2 0	0 2 2 1	0 2 3 3	0 2 3 6	0 2 3 7	0 2 4 8	0 2 4 9	0 3 0 0	0 3 3 4	0 3 3 7	0 3 4 4	0 3 4 7	0 3 4 8	0 3 4 9	0 3 5 3	0 3 5 6	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																											5
Hepatocellular carcinoma, multiple																											5
Hepatocellular adenoma		X			X	X	X	X			X						X										13
Hepatocellular adenoma, multiple				X									X			X		X				X	X	X	X		9
Hepatocholangiocarcinoma																											1
Mesentery										+									+	+				+			5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																					1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma															X												2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											2
Parathyroid gland	M	+	M	M	+	+	M	M	M	+	+	M	M	M	+	M	+	+	M	M	+	+	+	+	M		26
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Follicular cell, adenoma													X											X			2
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	3 7 4	4 5 9	5 5 6	5 6 1	5 6 5	6 1 8	6 2 1	6 4 2	6 6 3	6 6 7	6 6 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 1 4	0 5 0	0 1 8	0 2 2	0 1 0	0 4 0	0 3 3	0 3 9	0 1 5	0 1 7	0 0 2	0 0 5	0 0 6	0 0 7	0 1 2	0 1 9	0 2 4	0 2 5	0 3 1	0 3 2	0 3 5	0 3 6	0 3 8	0 4 1
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node							+	+																	
Schwannoma malignant, metastatic, spinal cord								X																	
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	
Hepatocholangiocarcinoma, metastatic, liver		X																							
Lymph node, mandibular	M	+	M	M	M	M	+	+	+	+	M	+	+	M	M	M	+	+	M	+	+	M	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Hepatocholangiocarcinoma, metastatic, liver		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prepuce, histiocytic sarcoma																					X				
Subcutaneous tissue, hemangiosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord								+																	
Schwannoma malignant								X																	
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X							X	X		X				X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma												X							X					X
Hepatocellular carcinoma, metastatic, liver	X			X	X	X			X	X				X											
Hepatocholangiocarcinoma, metastatic, liver		X																							
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	
Carcass ID Number	0 0 4 3	0 0 4 5	0 0 4 6	0 0 1 0 1	0 0 1 4	0 0 1 8	0 0 1 9	0 1 1 1	0 1 1 3	0 1 2 0	0 1 2 1	0 1 2 3	0 1 2 6	0 1 2 7	0 1 2 8	0 1 2 9	0 1 3 0	0 1 3 4	0 1 3 7	0 1 4 4	0 1 4 7	0 1 4 8	0 1 4 9	0 1 5 0	0 1 5 3	0 1 5 6	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											2
Schwannoma malignant, metastatic, spinal cord																											1
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	M	+	M	M	M	+	+	M	+	M	+	+	+	+	M	+		38
Hepatocholangiocarcinoma, metastatic, liver																											1
Lymph node, mandibular	M	+	M	+	+	M	+	M	M	M	+	+	M	M	+	M	M	M	M	M	+	+	+	M	M		24
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mediastinal	M	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+		40
Hepatocholangiocarcinoma, metastatic, liver																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		43
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Prepuce, histiocytic sarcoma																											1
Subcutaneous tissue, hemangiosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spinal cord																									+		2
Schwannoma malignant																											1
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma												X			X												7
Alveolar/bronchiolar adenoma, multiple		X									X																2
Alveolar/bronchiolar carcinoma					X																				X		5
Hepatocellular carcinoma, metastatic, liver																											7
Hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pleura								+																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

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

Number of Days on Study	3 7 4	4 5 9	5 5 6	5 6 1	5 6 5	6 1 8	6 2 1	6 4 2	6 6 3	6 6 7	6 6 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 1 4	0 5 0	0 1 8	0 2 2	0 1 0	0 4 0	0 3 3	0 3 9	0 1 5	0 1 7	0 0 2	0 0 5	0 0 6	0 0 7	0 1 2	0 1 9	0 2 4	0 2 5	0 3 1	0 3 2	0 3 5	0 3 6	0 3 8	0 4 1
Special Senses System																									
Ear																									
Eye																									
Harderian gland														+											
Adenoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymphoma malignant							X																		

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	
Carcass ID Number	0 4 3	0 4 5	0 4 6	0 0 1	0 0 4	0 0 8	0 0 9	0 1 1	0 1 3	0 2 0	0 2 1	0 2 3	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 4	0 3 7	0 4 4	0 4 7	0 4 8	0 4 9	0 3 3	0 1 6	Total Tissues/ Tumors	
Special Senses System																													
Ear					+																							1	
Eye													+															1	
Harderian gland													+							+								3	
Adenoma													X							X								3	
Urinary System																													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																												1	
Lymphoma malignant																												1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	5 4 9	6 1 1	6 2 1	6 4 9	6 5 6	6 7 0	6 8 1	6 8 1	7 0 1	7 0 5	7 0 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 1 5	2 1 6	2 3 4	2 1 1	2 0 7	2 4 8	2 1 4	2 4 9	2 2 8	2 3 3	2 2 9	2 0 2	2 0 4	2 0 6	2 0 9	2 1 8	2 1 9	2 2 3	2 2 4	2 2 5	2 2 7	2 3 2	2 3 6	2 3 7	2 3 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	M	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Hepatocellular carcinoma				X							X								X	X			X		
Hepatocellular carcinoma, multiple			X				X																		
Hepatocellular adenoma	X						X		X							X				X		X			
Hepatocellular adenoma, multiple					X						X			X							X		X		
Mesentery												+	+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth											+													+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Capsule, adenoma						X									X										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	M	M	M	M	M	+	+	+	M	+	+	M	M	+	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 3 9	2 4 3	2 4 6	2 5 0	2 0 1	2 0 3	2 0 5	2 0 8	2 1 2	2 1 3	2 1 7	2 2 1	2 2 2	2 2 6	2 3 0	2 3 1	2 3 5	2 4 0	2 4 1	2 4 2	2 4 4	2 4 5	2 1 0	2 2 0	2 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma						X			X						X											8
Hepatocellular carcinoma, multiple																	X									3
Hepatocellular adenoma								X				X							X	X						10
Hepatocellular adenoma, multiple			X			X															X					8
Mesentery																				+						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X																	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth														+			+									4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																	X									1
Capsule, adenoma																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	M	+	+	M	M	+	+	M	+	M	M	M	+	+	+	M	+	M	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma																			X							1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	5 4 9	6 1 1	6 2 1	6 4 9	6 5 6	6 7 0	6 8 1	6 8 1	7 0 1	7 0 5	7 0 7	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 1 5	2 1 6	2 3 4	2 1 1	2 0 7	2 4 8	2 1 4	2 4 9	2 2 8	2 3 3	2 2 9	2 0 2	2 0 4	2 0 6	2 0 9	2 1 8	2 1 9	2 2 3	2 2 4	2 2 5	2 2 7	2 3 2	2 3 6	2 3 7	2 3 8
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Lymph node		+																							
Lymph node, bronchial	M	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	M	+
Lymph node, mandibular	M	M	+	+	M	+	M	+	+	M	M	M	M	M	+	M	+	M	+	+	+	+	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	M	M	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Mast cell tumor NOS																									
Thymus	+	+	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X															X		X				X
Alveolar/bronchiolar carcinoma				X														X							
Hepatocellular carcinoma, metastatic, liver			X				X												X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland													+												
Adenoma													X												
Zymbal's gland																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant		X							X																

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 3 9	2 4 3	2 4 6	2 5 0	2 0 1	2 0 3	2 0 5	2 0 8	2 1 2	2 1 3	2 1 7	2 2 1	2 2 2	2 2 6	2 3 0	2 3 1	2 3 5	2 4 0	2 4 1	2 4 2	2 4 4	2 4 5	2 4 7	2 5 0	2 0 0	2 4 7	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Lymph node																											1
Lymph node, bronchial	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	M	M	M	+	+	+	+	+	+	+	M	35
Lymph node, mandibular	+	+	M	+	+	+	M	M	M	+	+	+	+	M	+	+	M	+	M	M	M	M	M	+	+	M	26
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	M	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	M	M	M	+	+	+	M	33
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Mast cell tumor NOS																							X				1
Thymus	+	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X							X				X			7
Alveolar/bronchiolar carcinoma																											2
Hepatocellular carcinoma, metastatic, liver						X											X										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland							+											+									3
Adenoma							X											X									3
Zymbal's gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																	X										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	4 2 1	4 3 0	4 5 7	5 0 2	5 1 1	5 3 7	5 6 3	5 6 7	5 8 2	5 8 3	5 8 3	5 8 5	5 9 7	6 0 0	6 1 8	6 4 7	6 5 5	6 6 3	6 7 0	6 8 1	6 9 8	7 0 4	7 0 5	7 2 9	7 2 9
Carcass ID Number	4 3 9	4 3 8	4 3 3	4 1 9	4 4 4	4 2 8	4 3 5	4 1 1	4 1 8	4 0 5	4 1 0	4 1 6	4 1 5	4 3 1	4 2 1	4 4 0	4 4 3	4 4 5	4 2 9	4 0 1	4 3 0	4 5 0	4 4 1	4 0 6	4 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	A	+	+	A	+	+	+	M	A	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	+	+	+	+	+	+	+	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	A	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+
Intestine small, ileum	A	+	A	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	A	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Hepatocellular carcinoma		X	X	X				X		X		X						X	X		X		X		
Hepatocellular carcinoma, multiple													X											X	
Hepatocellular adenoma									X					X		X				X				X	
Hepatocellular adenoma, multiple																									X
Mesentery													+												
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	A	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma											X														
Adrenal medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	M	+	M	M	+	+	M	+	M	M	+	M	+	+	+	M	M	+	M	M	+
Pituitary gland	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Testes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 0 8	4 1 7	4 2 0	4 2 2	4 2 5	4 3 2	4 3 7	4 4 2	4 4 7	4 4 9	4 0 2	4 0 4	4 0 9	4 1 2	4 1 3	4 1 4	4 2 6	4 2 7	4 3 6	4 4 6	4 4 8	4 0 3	4 2 3	4 2 4	4 3 4	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma											X														2
Hepatocellular carcinoma																		X				X			12
Hepatocellular carcinoma, multiple									X												X				4
Hepatocellular adenoma		X					X			X				X		X		X	X	X					13
Hepatocellular adenoma, multiple	X								X		X	X													5
Mesentery				+							+														3
Oral mucosa																		+							1
Squamous cell carcinoma																		X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangioma															X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																						X			1
Squamous cell papilloma														X								X			2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																X									2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	M	+	+	+	+	+	M	M	M	M	M	+	M	M	+	+	M	+	+	M	M	+	26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																								X	1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																								+	1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 0 8	4 1 7	4 2 0	4 2 2	4 2 5	4 3 2	4 3 7	4 4 2	4 4 7	4 4 9	4 0 2	4 0 4	4 0 9	4 1 2	4 1 3	4 1 4	4 2 6	4 2 7	4 3 6	4 4 6	4 4 8	4 0 3	4 2 3	4 2 4	4 3 4	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	33
Lymph node, mandibular	M	+	M	M	+	+	M	+	M	M	+	M	+	+	M	+	+	+	+	M	+	M	M	+	+	32
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	M	+	+	+	M	+	+	+	+	+	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	M	+	M	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	36
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma									X																	1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma	X						X			X																8
Alveolar/bronchiolar adenoma, multiple																						X				2
Alveolar/bronchiolar carcinoma		X																								2
Alveolar/bronchiolar carcinoma, multiple																		X								1
Hepatocellular carcinoma, metastatic, liver									X									X								5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																									
Eye																			+							1
Harderian gland												+							+							2
Adenoma												X							X							2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	0 7 3	3 1 2	3 6 8	3 7 4	4 0 2	4 4 2	4 5 4	5 9 6	6 0 4	6 1 3	6 1 4	6 2 3	6 2 9	6 3 8	6 6 3	6 6 5	6 7 0	6 7 0	6 8 4	6 8 4	6 9 4	6 9 4	7 0 2	7 1 1	7 2 9
Carcass ID Number	6 1 7	6 4 0	6 3 8	6 1 5	6 0 2	6 3 3	6 3 6	6 5 0	6 1 4	6 3 2	6 2 9	6 4 5	6 4 2	6 0 5	6 4 7	6 0 9	6 2 2	6 4 9	6 0 8	6 1 3	6 0 4	6 2 6	6 4 1	6 3 4	6 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	A	A	A	A	A	A	+	A	+	A	+	A	+	+	M	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	A	A	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	A	A	A	A	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	A	A	A	A	A	A	+	A	+	A	+	A	+	+	+	+	+	+	+	A	+
Histiocytic sarcoma													X												
Intestine small, ileum	+	A	A	A	A	A	A	A	A	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Hemangiosarcoma							X											X							
Hepatocellular carcinoma		X	X	X	X	X			X		X		X			X		X							X
Hepatocellular carcinoma, multiple										X					X				X					X	
Hepatocellular adenoma			X			X			X		X	X						X							X
Hepatocellular adenoma, multiple																				X					
Histiocytic sarcoma													X										X		
Mesentery													+												
Histiocytic sarcoma													X												
Pancreas	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Squamous cell papilloma					X																				
Stomach, glandular	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	M	+	+	+	M	+	M	M	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma									X																
General Body System																									
None																									

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	
Carcass ID Number	6 1 0	6 1 6	6 1 8	6 1 9	6 2 1	6 2 3	6 2 7	6 2 8	6 3 5	6 3 9	6 4 3	6 4 8	6 0 1	6 0 3	6 0 6	6 1 1	6 1 2	6 2 0	6 2 4	6 3 0	6 3 1	6 4 4	6 4 6	6 2 5	6 3 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, islets, pancreatic															X											1
Hemangiosarcoma										X									X							4
Hepatocellular carcinoma	X									X			X				X								X	16
Hepatocellular carcinoma, multiple												X														5
Hepatocellular adenoma		X			X	X	X									X				X		X				14
Hepatocellular adenoma, multiple												X					X									3
Histiocytic sarcoma																										2
Mesentery																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Squamous cell papilloma	X																									2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Carcinoma															X											1
Parathyroid gland	M	+	+	M	M	M	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	M	+	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

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

Number of Days on Study	0 7 3	3 1 2	3 6 8	3 7 4	4 0 2	4 4 2	4 5 4	5 9 6	6 0 4	6 1 3	6 1 4	6 2 3	6 2 9	6 3 8	6 6 3	6 6 5	6 7 0	7 7 0	7 8 4	8 8 4	8 9 4	9 9 4	7 0 2	7 1 1	7 2 9
Carcass ID Number	6 1 7	6 4 0	6 3 8	6 1 5	6 0 2	6 3 3	6 3 6	6 5 0	6 1 4	6 3 2	6 2 9	6 4 5	6 4 2	6 0 5	6 4 7	6 0 9	6 2 2	6 4 9	6 0 8	6 1 3	6 0 4	6 2 6	6 4 1	6 3 4	6 3 7
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma													X												
Leiomyoma																									
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Histiocytic sarcoma													X												
Lymph node									+																
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	M	+	M	M	+	+	+
Lymph node, mandibular	+	M	+	M	+	M	M	M	+	M	M	+	+	+	+	M	M	+	+	M	M	M	M	M	+
Lymph node, mesenteric	+	+	+	+	M	+	+	A	+	+	+	+	+	M	+	A	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma													X												
Lymph node, mediastinal	+	M	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma													X												
Spleen	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma													X												
Thymus	+	+	+	+	M	M	+	+	+	M	M	+	+	M	+	+	+	+	M	+	M	+	+	+	M
Histiocytic sarcoma													X												
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X										X		X				X				
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver																X								X	
Histiocytic sarcoma																							X		
Nose	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	
Carcass ID Number	6 1 0	6 1 6	6 1 8	6 1 9	6 2 1	6 2 3	6 2 7	6 2 8	6 3 5	6 3 9	6 4 3	6 4 8	6 0 1	6 0 3	6 0 6	6 1 1	6 1 2	6 2 0	6 2 4	6 3 0	6 3 1	6 4 4	6 4 6	6 2 5	6 3 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Histiocytic sarcoma																										1
Leiomyoma																			X							1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																						X			X	2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							2
Histiocytic sarcoma																										1
Lymph node																										1
Lymph node, bronchial	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+	M	M	M	+	+	+	35
Lymph node, mandibular	M	M	+	+	M	+	+	+	+	+	+	+	+	M	M	M	M	+	M	+	+	M	+	M	M	25
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Histiocytic sarcoma																										1
Lymph node, mediastinal	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	M	+	+	+	+	37
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																			X							1
Histiocytic sarcoma																										1
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	37
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X						X													X	X			8
Alveolar/bronchiolar carcinoma								X						X						X						3
Hepatocellular carcinoma, metastatic, liver												X														3
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

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

Number of Days on Study	0737	3132	3368	3474	4022	4422	4545	5996	6044	6113	6114	6233	6429	6638	6663	6705	7700	7884	8844	9944	9944	0242	1119	2919
Carcass ID Number	6117	6140	6308	6115	6102	6323	6336	6550	6014	6332	6229	6445	6422	6405	6447	6409	6202	6249	6013	6104	6026	6241	6344	6307
Special Senses System																								
Harderian gland																								
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X											
Urinary bladder	+	A	+	+	+	+	A	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X											
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X									X		

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

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	
Carcass ID Number	61 0	61 6	61 8	61 9	62 1	62 3	62 7	62 8	63 5	63 9	64 3	64 8	65 1	65 3	65 6	65 9	66 1	66 2	66 4	66 5	66 7	66 8	67 0	67 1	67 4	67 6	67 7	67 8	67 9	68 0	Total Tissues/ Tumors
Special Senses System																															
Harderian gland		+												+																	2
Adenoma		X												X																	2
Urinary System																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																															1
Systemic Lesions																															
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																															2

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	6.7%	6.4%	5.0%	5.1%
Terminal rate[c]	3/39 (8%)	3/39 (8%)	2/27 (7%)	2/26 (8%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Poly-3 test[d]	P=0.440N	P=0.640N	P=0.555N	P=0.559N
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	2/49 (4%)	4/49 (8%)
Adjusted rate	0.0%	2.1%	5.0%	10.0%
Terminal rate	0/39 (0%)	0/39 (0%)	1/27 (4%)	2/26 (8%)
First incidence (days)	—[e]	670	704	454
Poly-3 test	P=0.014	P=0.511	P=0.211	P=0.046
Liver: Hepatocellular Adenoma				
Overall rate	22/50 (44%)	18/50 (36%)	18/49 (37%)	17/49 (35%)
Adjusted rate	48.6%	37.2%	43.8%	40.3%
Terminal rate	21/39 (54%)	13/39 (33%)	14/27 (52%)	10/26 (39%)
First incidence (days)	642	549	582	368
Poly-3 test	P=0.345N	P=0.180N	P=0.407N	P=0.283N
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	11/50 (22%)	16/49 (33%)	21/49 (43%)
Adjusted rate	20.8%	22.9%	35.9%	45.9%
Terminal rate	3/39 (8%)	7/39 (18%)	5/27 (19%)	7/26 (27%)
First incidence (days)	374	621	430	312
Poly-3 test	P=0.002	P=0.500	P=0.080	P=0.007
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	30/50 (60%)	24/50 (48%)	31/49 (63%)	30/49 (61%)
Adjusted rate	61.9%	48.9%	67.5%	64.8%
Terminal rate	22/39 (56%)	17/39 (44%)	16/27 (59%)	14/26 (54%)
First incidence (days)	374	549	430	312
Poly-3 test	P=0.225	P=0.137N	P=0.362	P=0.469
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	9/50 (18%)	7/50 (14%)	10/49 (20%)	8/50 (16%)
Adjusted rate	19.9%	14.7%	24.2%	19.5%
Terminal rate	8/39 (21%)	6/39 (15%)	5/27 (19%)	4/26 (15%)
First incidence (days)	642	649	537	402
Poly-3 test	P=0.445	P=0.353N	P=0.413	P=0.591N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	3/49 (6%)	3/50 (6%)
Adjusted rate	11.1%	4.2%	7.6%	7.6%
Terminal rate	5/39 (13%)	1/39 (3%)	3/27 (11%)	3/26 (12%)
First incidence (days)	729 (T)	649	729 (T)	729 (T)
Poly-3 test	P=0.446N	P=0.195N	P=0.427N	P=0.429N

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	8/50 (16%)	12/49 (24%)	11/50 (22%)
Adjusted rate	30.9%	16.9%	29.0%	26.9%
Terminal rate	13/39 (33%)	7/39 (18%)	7/27 (26%)	7/26 (27%)
First incidence (days)	642	649	537	402
Poly-3 test	P=0.524	P=0.087N	P=0.515N	P=0.430N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate	2.2%	2.1%	5.0%	12.4%
Terminal rate	1/39 (3%)	0/39 (0%)	1/27 (4%)	3/26 (12%)
First incidence (days)	729 (T)	670	704	454
Poly-3 test	P=0.019	P=0.749N	P=0.459	P=0.079
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted rate	2.2%	2.1%	10.0%	12.4%
Terminal rate	1/39 (3%)	0/39 (0%)	3/27 (11%)	3/26 (12%)
First incidence (days)	729 (T)	670	704	454
Poly-3 test	P=0.020	P=0.749N	P=0.145	P=0.079
All Organs: Malignant Lymphoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.2%	6.3%	0.0%	0.0%
Terminal rate	0/39 (0%)	1/39 (3%)	0/27 (0%)	0/26 (0%)
First incidence (days)	621	611	—	—
Poly-3 test	P=0.179N	P=0.324	P=0.526N	P=0.527N
All Organs: Benign Neoplasms				
Overall rate	30/50 (60%)	28/50 (56%)	26/50 (52%)	28/50 (56%)
Adjusted rate	65.9%	57.2%	60.2%	63.4%
Terminal rate	28/39 (72%)	21/39 (54%)	17/27 (63%)	17/26 (65%)
First incidence (days)	642	549	537	368
Poly-3 test	P=0.534N	P=0.252N	P=0.361N	P=0.487N
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	16/50 (32%)	19/50 (38%)	28/50 (56%)
Adjusted rate	38.6%	32.4%	42.4%	59.4%
Terminal rate	10/39 (26%)	8/39 (21%)	7/27 (26%)	12/26 (46%)
First incidence (days)	374	549	430	312
Poly-3 test	P=0.008	P=0.332N	P=0.435	P=0.031

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	33/50 (66%)	36/50 (72%)	41/50 (82%)
Adjusted rate	84.9%	66.4%	76.1%	85.3%
Terminal rate	32/39 (82%)	24/39 (62%)	18/27 (67%)	21/26 (81%)
First incidence (days)	374	549	430	312
Poly-3 test	P=0.278	P=0.025N	P=0.192N	P=0.596

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4a
Historical Incidence of Forestomach Squamous Cell Papilloma in Chamber Control Male B6C3F$_1$ Mice[a]

	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
1,3-Butadiene	1/50
Acetonitrile	0/50
Chloroprene	1/50
Cobalt sulfate heptahydrate	0/50
Furfuryl alcohol	0/50
Hexachlorocyclopentadiene	0/50
Isobutene	1/50
Isobutyraldehyde	1/50
Molybdenum trioxide	0/50
Nitromethane	0/50
Ozone	0/50
Tetrahydrofuran	0/50
Overall Historical Incidence	
Total (%)	5/970 (0.5%)
Mean ± standard deviation	0.5% ± 0.9%
Range	0%-2%

[a] Data as of 16 October 1997; no carcinomas observed

TABLE C4b
Historical Incidence of Liver Neoplasms in Chamber Control Male B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories				
1,3-Butadiene	0/50	13/50	11/50	21/50
Acetonitrile	1/50	13/50	7/50	19/50
Chloroprene	2/50	22/50	24/50	43/50
Cobalt sulfate heptahydrate	2/50	22/50	23/50	38/50
Furfuryl alcohol	0/50	13/50	15/50	28/50
Hexachlorocyclopentadiene	0/50	19/50	7/50	24/50
Isobutene	1/50	20/50	13/50	30/50
Isobutyraldehyde	1/49	12/49	17/49	27/49
Molybdenum trioxide	0/50	20/50	12/50	30/50
Nitromethane	1/50	17/50	16/50	29/50
Ozone	0/50	23/50	12/50	30/50
Tetrahydrofuran	1/50	24/50	14/50	35/50
Overall Historical Incidence				
Total (%)	14/968 (1.5%)	302/968 (31.2%)	247/968 (25.5%)	503/968 (52.0%)
Mean ± standard deviation	1.5% ± 1.5%	31.3% ± 11.1%	25.7% ± 10.4%	52.2% ± 16.4%
Range	0%-4%	7%-48%	11%-48%	20%-86%

[a] Data as of 16 October 1997

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	8	13	10
Natural death	4	3	10	14
Survivors				
Terminal sacrifice	39	39	27	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(45)	(40)	(35)
Degeneration, hyaline		1 (2%)		
Inflammation		1 (2%)		
Intestine small, duodenum	(49)	(48)	(44)	(41)
Inflammation				1 (2%)
Epithelium, hyperplasia				1 (2%)
Peyer's patch, hyperplasia	1 (2%)			
Intestine small, jejunum	(48)	(47)	(43)	(38)
Peyer's patch, hyperplasia	1 (2%)			1 (3%)
Intestine small, ileum	(48)	(47)	(43)	(39)
Inflammation	1 (2%)			
Peyer's patch, hyperplasia	1 (2%)	1 (2%)		
Liver	(50)	(50)	(49)	(49)
Angiectasis			1 (2%)	
Basophilic focus			1 (2%)	3 (6%)
Clear cell focus	4 (8%)		5 (10%)	3 (6%)
Degeneration, fatty	1 (2%)	2 (4%)	4 (8%)	
Eosinophilic focus	14 (28%)	10 (20%)	18 (37%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hepatodiaphragmatic nodule			1 (2%)	
Infarct		1 (2%)		
Inflammation	6 (12%)	3 (6%)	6 (12%)	6 (12%)
Karyomegaly	2 (4%)			1 (2%)
Necrosis	6 (12%)	2 (4%)	7 (14%)	9 (18%)
Bile duct, cyst			1 (2%)	1 (2%)
Kupffer cell, pigmentation, hemosiderin			8 (16%)	30 (61%)
Oval cell, hyperplasia	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Mesentery	(5)	(3)	(3)	(1)
Angiectasis		1 (33%)		
Fat, necrosis	5 (100%)	2 (67%)	2 (67%)	
Pancreas	(50)	(50)	(47)	(47)
Atrophy	10 (20%)	4 (8%)	2 (4%)	4 (9%)
Cytoplasmic alteration	1 (2%)			1 (2%)
Degeneration, hyaline		1 (2%)		
Inflammation		1 (2%)		
Duct, cyst		1 (2%)		
Salivary glands	(50)	(50)	(48)	(50)
Inflammation		1 (2%)	1 (2%)	1 (2%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(49)	(48)
Cyst	1 (2%)			
Hyperplasia			1 (2%)	
Mineralization				1 (2%)
Ulcer	1 (2%)	2 (4%)	9 (18%)	3 (6%)
Epithelium, hyperplasia	1 (2%)	7 (14%)	16 (33%)	21 (44%)
Stomach, glandular	(50)	(50)	(46)	(47)
Degeneration, hyaline			1 (2%)	
Inflammation, suppurative	1 (2%)			
Mineralization	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Ulcer		1 (2%)	2 (4%)	
Epithelium, hyperplasia			4 (9%)	1 (2%)
Tooth		(4)		
Malformation		4 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	47 (94%)	48 (96%)	47 (94%)	47 (94%)
Artery, inflammation	1 (2%)			
Atrium, thrombosis	1 (2%)			1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Degeneration, cystic	1 (2%)			
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hyperplasia	5 (10%)	9 (18%)	9 (18%)	9 (18%)
Hypertrophy	38 (76%)	28 (56%)	27 (55%)	27 (54%)
Capsule, hyperplasia	2 (4%)			3 (6%)
Adrenal medulla	(49)	(50)	(49)	(49)
Hyperplasia	1 (2%)	2 (4%)		3 (6%)
Islets, pancreatic	(50)	(50)	(47)	(46)
Hyperplasia	6 (12%)	3 (6%)	2 (4%)	
Inflammation	1 (2%)			
Parathyroid gland	(26)	(29)	(26)	(31)
Cyst		1 (3%)		
Pituitary gland	(49)	(49)	(46)	(48)
Hemorrhage			1 (2%)	
Pars distalis, cyst	1 (2%)			
Pars distalis, hyperplasia	5 (10%)	1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(50)	(48)	(49)	(50)
Follicular cell, hyperplasia	5 (10%)	8 (17%)	6 (12%)	5 (10%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Granuloma sperm		1 (2%)		
Hyperplasia				1 (2%)
Inflammation	4 (8%)	4 (8%)	1 (2%)	4 (8%)
Inflammation, granulomatous			1 (2%)	
Penis			(1)	
Inflammation			1 (100%)	
Preputial gland	(49)	(49)	(49)	(49)
Ectasia	1 (2%)	1 (2%)		1 (2%)
Inflammation	2 (4%)	7 (14%)	6 (12%)	8 (16%)
Prostate	(49)	(49)	(48)	(45)
Inflammation		2 (4%)	3 (6%)	4 (9%)
Epithelium, hyperplasia			1 (2%)	1 (2%)
Seminal vesicle	(50)	(49)	(46)	(46)
Inflammation	1 (2%)		2 (4%)	3 (7%)
Testes	(50)	(50)	(49)	(50)
Atrophy	5 (10%)	4 (8%)	6 (12%)	4 (8%)
Mineralization			3 (6%)	
Interstitial cell, hyperplasia		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Fibrosis			1 (2%)	
Hyperplasia		1 (2%)	9 (18%)	5 (10%)
Thrombosis				1 (2%)
Lymph node	(2)	(1)		(1)
Renal, hyperplasia				1 (100%)
Lymph node, bronchial	(38)	(35)	(33)	(35)
Hyperplasia	2 (5%)		1 (3%)	
Lymph node, mandibular	(24)	(26)	(32)	(25)
Hyperplasia		1 (4%)	1 (3%)	1 (4%)
Lymph node, mesenteric	(50)	(50)	(47)	(43)
Amyloid deposition	1 (2%)			
Angiectasis	2 (4%)	2 (4%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)	3 (6%)	1 (2%)	
Hyperplasia	7 (14%)	7 (14%)	4 (9%)	4 (9%)
Spleen	(50)	(50)	(48)	(49)
Hematopoietic cell proliferation	12 (24%)	11 (22%)	26 (54%)	42 (86%)
Hyperplasia, lymphoid	5 (10%)	8 (16%)	3 (6%)	1 (2%)
Pigmentation, hemosiderin		6 (12%)	45 (94%)	44 (90%)
Thymus	(43)	(43)	(36)	(37)
Atrophy	1 (2%)	1 (2%)	1 (3%)	1 (3%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Granuloma			1 (2%)	
Inflammation		1 (2%)		
Pigmentation, melanin			1 (2%)	
Prepuce, hyperplasia			1 (2%)	2 (4%)
Prepuce, inflammation, chronic active	2 (4%)	3 (6%)	13 (27%)	8 (16%)
Prepuce, ulcer		3 (6%)	11 (22%)	8 (16%)
Subcutaneous tissue, inflammation, granulomatous			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	4 (8%)		1 (2%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Inflammation, chronic	1 (2%)			
Necrosis	1 (2%)			
Vacuolization cytoplasmic			1 (2%)	1 (2%)
Meninges, infiltration cellular, mononuclear cell	1 (2%)	1 (2%)		
Respiratory System				
Larynx	(50)	(50)	(48)	(49)
Inflammation, suppurative				1 (2%)
Squamous epithelium, hyperplasia		3 (6%)		
Lung	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hemorrhage	5 (10%)	5 (10%)	5 (10%)	3 (6%)
Infiltration cellular, histiocyte	6 (12%)	1 (2%)	4 (8%)	4 (8%)
Inflammation, chronic	1 (2%)		1 (2%)	
Pigmentation, hemosiderin	1 (2%)			
Alveolar epithelium, hyperplasia	6 (12%)	1 (2%)	2 (4%)	4 (8%)
Artery, inflammation				1 (2%)
Nose	(50)	(50)	(48)	(48)
Inflammation, suppurative	2 (4%)	6 (12%)	2 (4%)	2 (4%)
Polyp, inflammatory		1 (2%)	1 (2%)	
Glands, hyperplasia				1 (2%)
Olfactory epithelium, atrophy	4 (8%)	4 (8%)	3 (6%)	
Olfactory epithelium, degeneration, hyaline	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Respiratory epithelium, degeneration, hyaline	4 (8%)	10 (20%)	5 (10%)	5 (10%)
Respiratory epithelium, metaplasia, squamous		1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Special Senses System				
Ear	(1)			
Inflammation, granulomatous	1 (100%)			
Eye	(1)		(1)	
Cornea, inflammation, chronic			1 (100%)	
Urinary System				
Kidney	(50)	(50)	(47)	(50)
Glomerulosclerosis	4 (8%)	4 (8%)	11 (23%)	9 (18%)
Hydronephrosis	1 (2%)		6 (13%)	5 (10%)
Inflammation				1 (2%)
Inflammation, chronic active		1 (2%)	2 (4%)	4 (8%)
Metaplasia, osseous		2 (4%)		
Mineralization	1 (2%)			2 (4%)
Nephropathy	48 (96%)	45 (90%)	40 (85%)	37 (74%)
Capsule, inflammation				1 (2%)
Cortex, cyst	4 (8%)	1 (2%)		6 (12%)
Pelvis, inflammation, chronic active		1 (2%)	1 (2%)	
Renal tubule, hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Renal tubule, mineralization	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Renal tubule, necrosis	1 (2%)		1 (2%)	
Renal tubule, pigmentation				3 (6%)
Urinary bladder	(50)	(50)	(46)	(45)
Inflammation		2 (4%)	5 (11%)	4 (9%)
Transitional epithelium, hyperplasia		2 (4%)	1 (2%)	1 (2%)
Transitional epithelium, ulcer		1 (2%)	4 (9%)	2 (4%)

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

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death	1			
Moribund	14	16	12	10
Natural deaths	6	3	5	4
Survivors				
Terminal sacrifice	29	31	33	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(43)	(43)	(46)	(46)
Intestine small, duodenum	(45)	(49)	(47)	(47)
Polyp adenomatous			1 (2%)	
Intestine small, jejunum	(46)	(49)	(47)	(48)
Carcinoma	1 (2%)			
Intestine small, ileum	(46)	(50)	(47)	(48)
Carcinoma		1 (2%)		
Liver	(50)	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	7 (14%)	10 (20%)	11 (22%)	9 (18%)
Hepatocellular carcinoma, multiple	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Hepatocellular adenoma	9 (18%)	5 (10%)	5 (10%)	8 (16%)
Hepatocellular adenoma, multiple	7 (14%)	3 (6%)	2 (4%)	
Hepatocholangiocarcinoma	2 (4%)			1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Mesentery	(10)	(4)	(5)	(9)
Hemangioma	1 (10%)			
Hemangiosarcoma		1 (25%)		
Osteosarcoma			1 (20%)	
Sarcoma, metastatic, skin	2 (20%)			
Pancreas	(49)	(50)	(49)	(50)
Salivary glands	(48)	(50)	(49)	(50)
Parotid gland, hemangioma			1 (2%)	
Stomach, forestomach	(50)	(50)	(49)	(50)
Hemangioma	1 (2%)			
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		1 (2%)	2 (4%)	5 (10%)
Stomach, glandular	(48)	(50)	(49)	(49)
Tongue	(1)			(1)
Squamous cell carcinoma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma benign	3 (6%)	1 (2%)		1 (2%)
Bilateral, pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	2 (4%)	1 (2%)		
Pituitary gland	(50)	(49)	(48)	(49)
Pars distalis, adenoma	5 (10%)	8 (16%)	8 (17%)	4 (8%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(49)
Follicular cell, adenoma	1 (2%)	2 (4%)	5 (10%)	1 (2%)
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Ovary	(50)	(49)	(49)	(49)
Cystadenoma	2 (4%)	1 (2%)	3 (6%)	
Granulosa cell tumor benign				1 (2%)
Hemangioma	1 (2%)			
Teratoma benign			2 (4%)	
Teratoma malignant			1 (2%)	
Uterus	(50)	(50)	(49)	(50)
Adenoma		1 (2%)		
Hemangiosarcoma			2 (4%)	
Histiocytic sarcoma	1 (2%)	1 (2%)		
Polyp stromal	1 (2%)	2 (4%)	4 (8%)	2 (4%)
Sarcoma stromal			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	1 (2%)
Lymph node	(4)	(7)	(6)	(1)
Sarcoma, metastatic, skin	1 (25%)			
Renal, sarcoma, metastatic, skin	1 (25%)			
Renal, teratoma malignant, metastatic, ovary			1 (17%)	
Lymph node, bronchial	(41)	(39)	(41)	(37)
Hepatocholangiocarcinoma, metastatic, liver				1 (3%)
Lymph node, mandibular	(37)	(38)	(40)	(38)
Histiocytic sarcoma		1 (3%)		
Lymph node, mesenteric	(47)	(48)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Lymph node, mediastinal	(31)	(40)	(38)	(34)
Hepatocholangiocarcinoma, metastatic, liver				1 (3%)
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Thymus	(46)	(41)	(46)	(48)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		3 (6%)
Skin	(50)	(50)	(50)	(50)
Sebaceous gland, adenoma				1 (2%)
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma		1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma	2 (4%)	1 (2%)		
Subcutaneous tissue, sarcoma, multiple	1 (2%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Osteosarcoma	1 (2%)			
Skeletal muscle	(1)			
Hemangiosarcoma	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	2 (4%)	4 (8%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)			
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)	
Carcinoma, metastatic, harderian gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	3 (6%)	6 (12%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)	1 (2%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Mediastinum, osteosarcoma, metastatic, bone	1 (2%)			
Mediastinum, sarcoma, metastatic, skin	1 (2%)			
Nose	(50)	(50)	(49)	(50)
Special Senses System				
Harderian gland	(6)	(4)	(3)	(4)
Adenoma	4 (67%)	3 (75%)	2 (67%)	3 (75%)
Carcinoma	1 (17%)	1 (25%)	1 (33%)	2 (50%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Urinary bladder	(47)	(49)	(48)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)	2 (4%)	
Lymphoma malignant	7 (14%)	9 (18%)	10 (20%)	7 (14%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	38	38	35
Total primary neoplasms	76	63	76	52
Total animals with benign neoplasms	31	23	27	18
Total benign neoplasms	44	30	42	27
Total animals with malignant neoplasms	27	26	28	22
Total malignant neoplasms	32	33	34	25
Total animals with metastatic neoplasms	9	4	7	3
Total metastatic neoplasms	18	4	7	8

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

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

Number of Days on Study	3 7 6	5 2 1	5 6 1	5 6 5	5 7 2	5 7 7	5 8 6	5 9 0	6 0 6	6 1 1	6 2 1	6 4 5	6 4 9	6 8 9	7 0 0	7 1 3	7 1 5	7 1 5	7 2 1	7 2 5	7 3 0	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 3 8	1 1 1	1 1 9	1 2 1	1 3 2	1 1 6	1 4 2	1 0 3	1 4 9	1 3 5	1 0 8	1 1 8	1 3 6	1 2 6	1 0 7	1 2 8	1 4 6	1 4 7	1 2 5	1 2 0	1 3 1	1 0 4	1 0 6	1 1 0	1 1 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Carcinoma	X																								
Intestine small, ileum	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																		X		X		X			X
Hepatocellular carcinoma, multiple	X								X		X														
Hepatocellular adenoma							X				X			X				X							
Hepatocellular adenoma, multiple								X									X			X			X	X	
Hepatocholangiocarcinoma						X																			
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone																					X				
Mesentery		+					+		+			+	+												
Hemangioma																									
Sarcoma, metastatic, skin		X										X													
Pancreas	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Stomach, glandular	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue													+												
Squamous cell carcinoma													X												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	+	+	+	M	M	M	+	M	+	M	+	+	M	M	+	M	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X															X			X			
Pars distalis, carcinoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
General Body System																									
None																									

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

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 1 4	1 1 7	1 2 2	1 3 4	1 5 0	1 0 1	1 0 2	1 0 5	1 0 9	1 1 5	1 2 3	1 2 7	1 2 9	1 3 0	1 3 3	1 4 1	1 4 3	1 4 4	1 4 5	1 4 8	1 1 3	1 2 4	1 3 7	1 3 9	1 4 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																X	X								7
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma		X				X				X						X							X			9
Hepatocellular adenoma, multiple															X			X								7
Hepatocholangiocarcinoma																						X				2
Histiocytic sarcoma						X																				1
Osteosarcoma, metastatic, bone																										1
Mesentery								+					+		+		+					+				10
Hemangioma													X													1
Sarcoma, metastatic, skin																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X						X											3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X								X													2
Parathyroid gland	M	M	M	M	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma										X			X													5
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										

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

Number of Days on Study	3 7 6	5 2 1	5 6 1	5 6 5	5 7 2	5 7 7	5 8 6	5 9 0	6 0 6	6 1 1	6 2 1	6 4 5	6 4 9	6 8 9	7 0 0	7 1 3	7 1 5	7 1 5	7 2 1	7 2 5	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 3 8	1 1 1	1 1 9	1 2 1	1 3 2	1 1 6	1 4 2	1 0 3	1 4 9	1 3 5	1 0 8	1 1 8	1 3 6	1 2 6	1 0 7	1 2 8	1 4 6	1 4 7	1 2 5	1 2 0	1 3 1	1 0 4	1 0 6	1 1 0	1 1 2
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+	M	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																			X						X
Hemangioma					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Lymph node					+							+													
Sarcoma, metastatic, skin												X													
Renal, sarcoma, metastatic, skin												X													
Lymph node, bronchial	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	+	+
Lymph node, mandibular	+	M	+	+	M	+	+	M	+	+	+	+	M	M	+	M	+	M	+	+	+	M	M	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver						X																			
Sarcoma, metastatic, skin												X													
Lymph node, mediastinal	M	+	M	M	+	+	M	+	M	+	M	+	+	+	+	M	+	+	+	+	M	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma												X					X								
Subcutaneous tissue, sarcoma, multiple		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Osteosarcoma																					X				
Skeletal muscle														+											
Hemangiosarcoma														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																X									

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 1 4	1 1 7	1 2 2	1 3 4	1 5 0	1 0 1	1 0 2	1 0 5	1 0 9	1 1 5	1 2 3	1 2 7	1 2 9	1 3 0	1 3 3	1 4 1	1 4 3	1 4 4	1 4 5	1 4 8	1 1 3	1 2 4	1 3 7	1 3 9	1 4 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	41
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										2
Hemangioma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Polyp stromal																	X									1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node								+																+		4
Sarcoma, metastatic, skin																										1
Renal, sarcoma, metastatic, skin																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	41
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	37
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic liver																										1
Sarcoma, metastatic, skin																										1
Lymph node, mediastinal	+	M	M	+	+	M	+	+	M	+	+	+	M	M	M	+	+	+	+	M	+	M	+	+	M	31
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Histiocytic sarcoma						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										2
Subcutaneous tissue, sarcoma multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Osteosarcoma																										1
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1

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

Number of Days on Study	3 7 6	5 2 1	5 6 1	5 6 5	5 7 2	5 7 7	5 8 6	5 9 0	6 0 6	6 1 1	6 2 1	6 4 5	6 4 9	6 8 9	7 0 0	7 1 3	7 1 5	7 1 5	7 2 1	7 2 5	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 3 8	1 1 1	1 1 9	1 2 1	1 3 2	1 1 6	1 4 2	1 0 3	1 4 9	1 3 5	1 0 8	1 1 8	1 3 6	1 2 6	1 0 7	1 2 8	1 4 6	1 4 7	1 2 5	1 2 0	1 3 1	1 0 4	1 0 6	1 1 0	1 1 2
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar adenoma, multiple																						X			
Hepatocellular carcinoma, metastatic, liver	X										X							X							
Hepatocholangiocarcinoma, metastatic, liver						X																			
Osteosarcoma, metastatic, bone																					X				
Sarcoma, metastatic, skin												X													
Mediastinum, osteosarcoma, metastatic, bone																					X				
Mediastinum, sarcoma, metastatic, skin												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland																							+		
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver						X																			
Urinary bladder	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant					X														X				X		

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 1 4	1 1 7	1 2 2	1 3 4	1 5 0	1 0 1	1 0 2	1 0 5	1 0 9	1 1 5	1 2 3	1 2 7	1 2 9	1 3 0	1 3 3	1 4 1	1 4 3	1 4 4	1 4 5	1 4 8	1 1 3	1 2 4	1 3 7	1 3 9	1 4 0	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X					X			X									X							5
Alveolar/bronchiolar adenoma, multiple									X																	2
Hepatocellular carcinoma, metastatic, liver	X																									4
Hepatocholangiocarcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, bone																										1
Sarcoma, metastatic, skin																										1
Mediastinum, osteosarcoma, metastatic, bone																										1
Mediastinum, sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye													+													1
Harderian gland						+						+	+			+					+					6
Adenoma						X						X				X					X					4
Carcinoma													X													1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Lymphoma malignant				X				X									X							X		7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	34 0	34 3	34 9	30 5	30 7	31 1	31 4	31 9	32 1	32 3	33 3	33 4	33 7	33 8	34 1	34 2	34 5	34 8	35 0	30 1	31 6	32 0	32 5	32 7	33 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Hepatocellular carcinoma				X										X												10
Hepatocellular carcinoma, multiple																						X				2
Hepatocellular adenoma													X			X								X		5
Hepatocellular adenoma, multiple																						X				3
Histiocytic sarcoma																										1
Mesentery																			+							4
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Parathyroid gland	+	M	+	+	M	+	M	+	+	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	M	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X										X			X			X		X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
Follicular cell, carcinoma				X																						1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	2 5 5	3 6 9	3 7 2	4 5 6	4 7 2	5 3 4	5 4 4	5 9 2	6 0 4	6 0 6	6 4 7	6 7 0	6 7 2	6 7 6	6 9 4	7 1 2	7 1 2	7 1 5	7 2 3	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 4 6	3 1 2	3 3 0	3 3 2	3 2 2	3 0 3	3 4 4	3 1 8	3 0 6	3 1 3	3 2 8	3 0 8	3 1 7	3 3 9	3 4 7	3 0 2	3 2 4	3 1 5	3 2 6	3 0 4	3 0 9	3 1 0	3 2 9	3 3 1	3 3 5
Genital System																									
Clitoral gland	M	+	+	M	+	+	+	M	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Histiocytic sarcoma										X															
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+	+				+						+		+				
Lymph node, bronchial	M	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	+	M	M
Histiocytic sarcoma										X															
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mediastinal	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	M	+	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, sarcoma											X														
Subcutaneous tissue, sarcoma, multiple		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord									+																
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma														X											
Hepatocellular carcinoma, metastatic, liver								X									X	X							
Histiocytic sarcoma										X															
Sarcoma, metastatic, skin		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	340	343	349	355	360	371	374	391	401	423	433	434	437	438	441	442	445	448	450	461	462	463	465	466	467	476	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma															X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																	1
Histiocytic sarcoma																											1
Polyp stromal													X				X										2
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+									+										7
Lymph node, bronchial	+	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+		39
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	M	+	M	+		38
Histiocytic sarcoma																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+		40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	41
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma					X																						1
Subcutaneous tissue, sarcoma																											1
Subcutaneous tissue, sarcoma, multiple																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																											1
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X									X					2
Alveolar/bronchiolar carcinoma		X																									2
Hepatocellular carcinoma, metastatic, liver																											3
Histiocytic sarcoma																											1
Sarcoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	2 5 5	3 6 9	3 7 2	4 5 6	4 7 2	5 3 4	5 4 4	5 9 2	6 0 4	6 0 6	6 4 7	6 7 0	6 7 2	6 7 6	6 9 4	7 1 2	7 1 2	7 1 5	7 2 3	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 4 6	3 1 2	3 3 0	3 3 2	3 2 2	3 0 3	3 4 4	3 1 8	3 0 6	3 1 3	3 2 8	3 0 8	3 1 7	3 3 9	3 4 7	3 0 2	3 2 4	3 1 5	3 2 6	3 0 4	3 0 9	3 1 0	3 2 9	3 3 1	3 3 5
Special Senses System																									
Harderian gland																							+		
Adenoma																							X		
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant							X		X				X						X		X	X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 62.5 ppm

Number of Days on Study	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	
Carcass ID Number	340	343	349	005	007	011	014	019	021	023	033	034	037	038	041	042	045	048	050	101	106	120	125	127	136	Total Tissues/ Tumors
Special Senses System																											
Harderian gland							+																	+	+	4
Adenoma							X																		X	3
Carcinoma																								X		1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Lymphoma malignant							X	X																	X	9	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	0 7 2	1 9 6	3 9 7	4 0 8	4 5 6	5 3 7	5 4 4	5 7 0	5 7 2	5 9 1	6 2 7	6 6 6	6 9 8	7 1 5	7 2 3	7 2 3	7 2 3	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	5 4 9	5 0 3	5 2 5	5 2 9	5 1 8	5 2 4	5 0 2	5 2 7	5 1 4	5 1 9	5 1 6	5 4 2	5 0 6	5 1 0	5 1 2	5 3 0	5 3 4	5 0 7	5 0 9	5 1 3	5 1 5	5 1 7	5 2 6	5 3 1	5 3 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X				X									X			X	X	X	
Hepatocellular carcinoma, multiple							X																		
Hepatocellular adenoma														X								X			
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma												X													
Mesentery										+			+												
Osteosarcoma													X												
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parotid gland, hemangioma																									
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel												A													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X											X					X	
Pars intermedia, adenoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	+	M	M	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																							X	X	
Teratoma benign		X																							
Teratoma malignant	X																								
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Polyp stromal															X						X				
Sarcoma stromal															X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 3 6	5 3 7	5 4 1	5 4 6	5 4 7	5 0 1	5 0 5	5 1 1	5 2 0	5 2 1	5 2 2	5 3 2	5 3 3	5 3 9	5 4 0	5 4 3	5 4 5	5 5 0	5 0 4	5 0 8	5 2 3	5 2 8	5 3 8	5 4 4	5 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Polyp adenomatous																							X			1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma					X					X						X			X					X		11
Hepatocellular carcinoma, multiple	X																									2
Hepatocellular adenoma									X		X											X				5
Hepatocellular adenoma, multiple																					X			X		2
Histiocytic sarcoma																										1
Mesentery	+											+			+											5
Osteosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parotid gland, hemangioma																									X	1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																	X			X						2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma							X	X									X					X		X		8
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X							X					X				X	X				5
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	M	+	+	M	+	+	38
Ovary	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma	X																									3
Teratoma benign																	X									2
Teratoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																	X									2
Polyp stromal				X																X						4
Sarcoma stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol: 125 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 3 6	5 3 7	5 4 1	5 4 6	5 4 7	5 0 1	5 0 5	5 1 1	5 2 0	5 2 1	5 2 2	5 3 2	5 3 3	5 3 9	5 4 0	5 4 3	5 4 5	5 5 0	5 0 4	5 0 8	5 2 3	5 2 8	5 3 8	5 4 4	5 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Lymph node															+											6
Renal, teratoma malignant, metastatic, ovary																										1
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma				X																						1
Lymph node, mediastinal	M	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, hemangiosarcoma					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X													X			4
Alveolar/bronchiolar carcinoma		X																								1
Hepatocellular carcinoma, metastatic, liver	X				X																					6
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland			+																							3
Adenoma			X																							2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma				X																						2
Lymphoma malignant							X	X		X					X										X	10

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

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

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 3 5	7 4 3	7 4 4	7 4 5	7 4 8	7 0 2	7 0 4	7 0 5	7 1 4	7 1 6	7 2 1	7 2 5	7 2 6	7 3 0	7 3 7	7 3 8	7 4 1	7 4 9	7 5 0	7 0 6	7 1 9	7 3 1	7 3 6	7 4 2	7 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X										X				X										9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X			X							X		X					X			X					8
Hepatocholangiocarcinoma																										1
Mesentery		+							+			+				+										9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma											X															1
Squamous cell papilloma													X									X				5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																							+			1
Cardiovascular System																										
Blood vessel																	+									2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																			X							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Pars distalis, adenoma				X	X																					4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Follicular cell, adenoma				X																						1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																	X		X							2

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

Number of Days on Study	4 3 7	4 8 5	4 8 9	5 2 9	5 8 2	5 8 2	6 1 8	6 2 1	6 5 3	6 5 6	6 5 6	6 6 0	6 8 2	7 0 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 1 0	7 0 3	7 3 9	7 1 1	7 3 4	7 4 0	7 1 5	7 1 8	7 0 7	7 2 7	7 4 7	7 2 4	7 0 8	7 3 2	7 0 1	7 0 9	7 1 2	7 1 3	7 1 7	7 2 0	7 2 2	7 2 3	7 2 8	7 2 9	7 3 3
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node				+																					
Lymph node, bronchial	M	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M
Hepatocholangiocarcinoma, metastatic, liver			X																						
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	M	+	M
Hepatocholangiocarcinoma, metastatic, liver			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Hepatocholangiocarcinoma, metastatic, liver			X																						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X						X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, harderian gland										X															
Hepatocellular carcinoma, metastatic, liver																				X					
Hepatocholangiocarcinoma, metastatic, liver			X																						
Mediastinum, hepatocholangiocarcinoma, metastatic, liver			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye										+	+														
Harderian gland										+	+														
Adenoma										X															
Carcinoma										X	X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant	X			X		X						X							X						X

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

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 3 5	7 4 3	7 4 4	7 4 5	7 4 8	7 0 2	7 0 4	7 0 5	7 1 4	7 1 6	7 2 1	7 2 5	7 2 6	7 3 0	7 3 7	7 3 8	7 4 1	7 4 9	7 5 0	7 0 6	7 1 9	7 3 1	7 3 6	7 4 2	7 4 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Lymph node																										1
Lymph node, bronchial	M	M	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	37
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	M	+	M	M	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	38
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	M	+	M	+	M	M	M	+	+	+	M	+	M	+	+	+	+	M	+	+	M	M	+	+	34
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X			3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma																X										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																					1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye					+						+															4
Harderian gland					+						+															4
Adenoma					X						X															3
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																				X						7

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	1/50 (2%)	1/49 (2%)	1/50 (2%)
Adjusted rate[b]	7.0%	2.4%	2.4%	2.3%
Terminal rate[c]	2/29 (7%)	0/31 (0%)	1/33 (3%)	1/36 (3%)
First incidence (days)	713	592	731 (T)	731 (T)
Poly-3 test[d]	P=0.238N	P=0.311N	P=0.321N	P=0.297N
Harderian Gland: Adenoma				
Overall rate	4/50 (8%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate	9.3%	7.2%	4.8%	6.8%
Terminal rate	4/29 (14%)	3/31 (10%)	2/33 (6%)	2/36 (6%)
First incidence (days)	731 (T)	731 (T)	731 (T)	656
Poly-3 test	P=0.405N	P=0.514N	P=0.348N	P=0.484N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	4/50 (8%)
Adjusted rate	11.6%	9.5%	7.1%	9.0%
Terminal rate	5/29 (17%)	4/31 (13%)	3/33 (9%)	2/36 (6%)
First incidence (days)	731 (T)	731 (T)	731 (T)	656
Poly-3 test	P=0.408N	P=0.516N	P=0.369N	P=0.478N
Liver: Hepatocellular Adenoma				
Overall rate	16/50 (32%)	8/50 (16%)	7/49 (14%)	8/50 (16%)
Adjusted rate	35.8%	18.7%	16.7%	18.0%
Terminal rate	9/29 (31%)	5/31 (16%)	6/33 (18%)	7/36 (19%)
First incidence (days)	586	456	715	582
Poly-3 test	P=0.048N	P=0.057N	P=0.035N	P=0.045N
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	12/50 (24%)	13/49 (27%)	10/50 (20%)
Adjusted rate	22.3%	27.5%	29.8%	21.9%
Terminal rate	5/29 (17%)	5/31 (16%)	10/33 (30%)	5/36 (14%)
First incidence (days)	376	592	537	582
Poly-3 test	P=0.483N	P=0.375	P=0.288	P=0.583N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	22/50 (44%)	16/50 (32%)	18/49 (37%)	18/50 (36%)
Adjusted rate	47.8%	36.1%	41.2%	39.1%
Terminal rate	13/29 (45%)	8/31 (26%)	14/33 (42%)	12/36 (33%)
First incidence (days)	376	456	537	582
Poly-3 test	P=0.307N	P=0.175N	P=0.336N	P=0.260N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	7/50 (14%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted rate	16.3%	4.8%	9.5%	2.3%
Terminal rate	7/29 (24%)	2/31 (7%)	2/33 (6%)	1/36 (3%)
First incidence (days)	731 (T)	731 (T)	715	731 (T)
Poly-3 test	P=0.032N	P=0.083N	P=0.272N	P=0.027N

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/50 (14%)	4/50 (8%)	5/50 (10%)	1/50 (2%)
Adjusted rate	16.3%	9.5%	11.9%	2.3%
Terminal rate	7/29 (24%)	3/31 (10%)	3/33 (9%)	1/36 (3%)
First incidence (days)	731 (T)	676	715	731 (T)
Poly-3 test	P=0.027N	P=0.271N	P=0.394N	P=0.027N
Mammary Gland: Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	2.4%	0.0%	6.7%
Terminal rate	0/29 (0%)	0/31 (0%)	0/33 (0%)	1/36 (3%)
First incidence (days)	—[e]	694	—	621
Poly-3 test	P=0.045	P=0.495	—[f]	P=0.125
Ovary: Cystadenoma				
Overall rate	2/50 (4%)	1/49 (2%)	3/49 (6%)	0/49 (0%)
Adjusted rate	4.6%	2.4%	7.3%	0.0%
Terminal rate	1/29 (3%)	1/31 (3%)	3/32 (9%)	0/35 (0%)
First incidence (days)	721	731 (T)	731 (T)	—
Poly-3 test	P=0.236N	P=0.514N	P=0.477	P=0.237N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	5/50 (10%)	8/49 (16%)	8/48 (17%)	4/49 (8%)
Adjusted rate	11.5%	19.6%	18.9%	9.2%
Terminal rate	3/29 (10%)	8/30 (27%)	7/33 (21%)	2/35 (6%)
First incidence (days)	565	731 (T)	570	660
Poly-3 test	P=0.334N	P=0.233	P=0.255	P=0.502N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	8/49 (16%)	8/48 (17%)	4/49 (8%)
Adjusted rate	13.7%	19.6%	18.9%	9.2%
Terminal rate	3/29 (10%)	8/30 (27%)	7/33 (21%)	2/35 (6%)
First incidence (days)	565	731 (T)	570	660
Poly-3 test	P=0.251N	P=0.335	P=0.361	P=0.372N
Skin: Sarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.8%	4.6%	0.0%	0.0%
Terminal rate	0/29 (0%)	0/31 (0%)	0/33 (0%)	0/36 (0%)
First incidence (days)	521	369	—	—
Poly-3 test	P=0.039N	P=0.510N	P=0.127N	P=0.118N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted rate	0.0%	2.4%	4.8%	11.2%
Terminal rate	0/29 (0%)	1/31 (3%)	2/33 (6%)	3/36 (8%)
First incidence (days)	—	731 (T)	731 (T)	582
Poly-3 test	P=0.008	P=0.495	P=0.231	P=0.034

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Stomach (Forestomach): Squamous Cell Papilloma or Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted rate	0.0%	2.4%	4.8%	13.4%
Terminal rate	0/29 (0%)	1/31 (3%)	2/33 (6%)	4/36 (11%)
First incidence (days)	—	731 (T)	731 (T)	582
Poly-3 test	P=0.002	P=0.495	P=0.231	P=0.017
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	2/50 (4%)	5/50 (10%)	1/49 (2%)
Adjusted rate	2.3%	4.8%	11.9%	2.3%
Terminal rate	1/29 (3%)	1/31 (3%)	5/33 (15%)	1/35 (3%)
First incidence (days)	731 (T)	712	731 (T)	731 (T)
Poly-3 test	P=0.581	P=0.492	P=0.095	P=0.761N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	5/50 (10%)	1/49 (2%)
Adjusted rate	2.3%	7.1%	11.9%	2.3%
Terminal rate	1/29 (3%)	2/31 (7%)	5/33 (15%)	1/35 (3%)
First incidence (days)	731 (T)	712	731 (T)	731 (T)
Poly-3 test	P=0.537N	P=0.296	P=0.095	P=0.761N
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.3%	4.8%	9.5%	4.5%
Terminal rate	1/29 (3%)	2/31 (7%)	3/33 (9%)	2/36 (6%)
First incidence (days)	731 (T)	731 (T)	723	731 (T)
Poly-3 test	P=0.406	P=0.491	P=0.171	P=0.508
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.3%	4.8%	9.5%	4.5%
Terminal rate	1/29 (3%)	2/31 (7%)	3/33 (9%)	2/36 (6%)
First incidence (days)	731 (T)	731 (T)	723	731 (T)
Poly-3 test	P=0.406	P=0.491	P=0.171	P=0.508
All Organs: Hemangioma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.9%	0.0%	4.7%	0.0%
Terminal rate	1/29 (3%)	0/31 (0%)	1/33 (3%)	0/36 (0%)
First incidence (days)	572	—	591	—
Poly-3 test	P=0.118N	P=0.126N	P=0.513N	P=0.117N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.6%	4.7%	7.1%	2.3%
Terminal rate	1/29 (3%)	1/31 (3%)	3/33 (9%)	1/36 (3%)
First incidence (days)	689	670	731 (T)	731 (T)
Poly-3 test	P=0.392N	P=0.686	P=0.487	P=0.493N

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	5/50 (10%)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted rate	11.4%	4.7%	11.8%	2.3%
Terminal rate	2/29 (7%)	1/31 (3%)	4/33 (12%)	1/36 (3%)
First incidence (days)	572	670	591	731 (T)
Poly-3 test	P=0.124N	P=0.231N	P=0.611	P=0.100N
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	9/50 (18%)	10/50 (20%)	7/50 (14%)
Adjusted rate	16.1%	20.8%	23.0%	15.2%
Terminal rate	5/29 (17%)	5/31 (16%)	5/33 (15%)	3/36 (8%)
First incidence (days)	572	544	397	437
Poly-3 test	P=0.448N	P=0.384	P=0.292	P=0.568N
All Organs: Benign Neoplasms				
Overall rate	31/50 (62%)	23/50 (46%)	27/50 (54%)	18/50 (36%)
Adjusted rate	67.4%	53.0%	61.3%	39.8%
Terminal rate	19/29 (66%)	18/31 (58%)	22/33 (67%)	14/36 (39%)
First incidence (days)	565	456	196	582
Poly-3 test	P=0.007N	P=0.112N	P=0.345N	P=0.005N
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	26/50 (52%)	28/50 (56%)	22/50 (44%)
Adjusted rate	56.9%	56.4%	60.2%	45.3%
Terminal rate	12/29 (41%)	12/31 (39%)	17/33 (52%)	11/36 (31%)
First incidence (days)	376	369	72	437
Poly-3 test	P=0.132N	P=0.563N	P=0.456	P=0.172N
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	38/50 (76%)	38/50 (76%)	35/50(70%)
Adjusted rate	87.7%	81.1%	80.0%	71.0%
Terminal rate	24/29 (83%)	23/31 (74%)	26/33 (79%)	22/36 (61%)
First incidence (days)	376	369	72	437
Poly-3 test	P=0.023N	P=0.268N	P=0.219N	P=0.033N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

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

	Incidence in Controls		
	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	0/50	0/50	0/50
Acetonitrile	1/49	0/49	1/49
Chloroprene	0/50	1/50	1/50
Cobalt sulfate heptahydrate	1/50	0/50	1/50
Furfuryl alcohol	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/49	0/49	0/49
Isobutene	0/50	0/50	0/50
Isobutyraldehyde	0/50	0/50	0/50
Molybdenum trioxide	0/50	0/50	0/50
Nitromethane	1/50	0/50	1/50
Ozone	0/50	0/50	0/50
Tetrahydrofuran	1/50	0/50	1/50
Overall Historical Incidence			
Total (%)	7/973 (0.7%)	2/973 (0.2%)	9/973 (0.9%)
Mean ± standard deviation	0.7% ± 1.0%	0.2% ± 0.6%	0.9% ± 1.1%
Range	0%-2%	0%-2%	0%-3%

[a] Data as of 16 October 1997

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

	Incidence in Controls			
	Hemangiosarcoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories				
1,3-Butadiene	1/49	11/49	4/49	15/49
Acetonitrile	0/49	4/49	7/49	9/49
Chloroprene	1/50	17/50	4/50	20/50
Cobalt sulfate heptahydrate	1/50	8/50	12/50	18/50
Furfuryl alcohol	0/50	7/50	9/50	14/50
Hexachlorocyclopentadiene	0/49	5/49	4/49	9/49
Isobutene	0/47	20/47	5/47	23/47
Isobutyraldehyde	1/49	9/49	6/49	12/49
Molybdenum trioxide	0/50	9/50	19/50	23/50
Nitromethane	2/50	14/50	10/50	19/50
Ozone	0/50	20/50	15/50	27/50
Tetrahydrofuran	0/50	12/50	6/50	17/50
Overall Historical Incidence				
Total (%)	8/968 (0.8%)	191/968 (19.7%)	149/968 (15.4%)	302/968 (31.2%)
Mean ± standard deviation	0.8% ± 1.3%	19.8% ± 10.2%	15.4% ± 8.1%	31.3% ± 10.6%
Range	0%-4%	8%-43%	8%-38%	18%-54%

[a] Data as of 16 October 1997

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

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death	1			
Moribund	14	16	12	10
Natural deaths	6	3	5	4
Survivors				
Terminal sacrifice	29	31	33	36
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Epithelium, hyperplasia	1 (2%)			
Intestine large, colon	(49)	(50)	(48)	(50)
Inflammation			1 (2%)	
Epithelium, hyperplasia			1 (2%)	
Intestine large, cecum	(49)	(50)	(47)	(48)
Epithelium, hyperplasia	1 (2%)			
Intestine small, duodenum	(45)	(49)	(47)	(47)
Inflammation		2 (4%)		
Necrosis		1 (2%)		
Epithelium, hyperplasia	1 (2%)	2 (4%)		2 (4%)
Intestine small, jejunum	(46)	(49)	(47)	(48)
Inflammation				1 (2%)
Necrosis				1 (2%)
Intestine small, ileum	(46)	(50)	(47)	(48)
Peyer's patch, hyperplasia				1 (2%)
Liver	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)		2 (4%)
Basophilic focus	1 (2%)			1 (2%)
Clear cell focus	2 (4%)	1 (2%)		1 (2%)
Degeneration, fatty	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	10 (20%)	6 (12%)	10 (20%)	5 (10%)
Hematopoietic cell proliferation	5 (10%)	7 (14%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)		
Infarct			1 (2%)	
Inflammation	3 (6%)	5 (10%)	4 (8%)	4 (8%)
Necrosis	2 (4%)	8 (16%)	7 (14%)	3 (6%)
Thrombosis			1 (2%)	
Bile duct, cyst	1 (2%)			
Endothelial cell, hyperplasia			1 (2%)	
Kupffer cell, pigmentation, hemosiderin		5 (10%)	25 (51%)	44 (88%)
Mesentery	(10)	(4)	(5)	(9)
Fat, necrosis	7 (70%)	3 (75%)	4 (80%)	9 (100%)
Pancreas	(49)	(50)	(49)	(50)
Atrophy	6 (12%)	4 (8%)	2 (4%)	8 (16%)
Cytoplasmic alteration	1 (2%)	2 (4%)		2 (4%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation			3 (6%)	
Duct, cyst		1 (2%)		1 (2%)
Duct, inflammation		1 (2%)		

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(49)	(50)
Cyst epithelial inclusion				1 (2%)
Erosion	1 (2%)			
Ulcer	1 (2%)	7 (14%)	13 (27%)	22 (44%)
Epithelium, hyperplasia	6 (12%)	27 (54%)	42 (86%)	44 (88%)
Stomach, glandular	(48)	(50)	(49)	(49)
Inflammation, suppurative		1 (2%)		
Mineralization		1 (2%)		
Ulcer	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Epithelium, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Tongue	(1)			(1)
Epithelium, hyperplasia				1 (100%)
Tooth		(1)		
Inflammation		1 (100%)		
Cardiovascular System				
Blood vessel		(1)		(2)
Inflammation				1 (50%)
Mineralization		1 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	46 (92%)	45 (90%)	44 (88%)	45 (90%)
Mineralization		1 (2%)		
Artery, inflammation				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Degeneration, cystic				2 (4%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		
Hyperplasia	1 (2%)			
Hypertrophy	3 (6%)	2 (4%)	6 (12%)	5 (10%)
Capsule, hyperplasia			1 (2%)	
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	1 (2%)			
Pituitary gland	(50)	(49)	(48)	(49)
Pars distalis, angiectasis	1 (2%)	4 (8%)		
Pars distalis, hyperplasia	15 (30%)	15 (31%)	16 (33%)	20 (41%)
Pars intermedia, hyperplasia	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
Inflammation		1 (2%)		
Follicle, cyst				1 (2%)
Follicular cell, hyperplasia	11 (22%)	8 (16%)	11 (22%)	11 (22%)
General Body System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Genital System				
Ovary	(50)	(49)	(49)	(49)
Angiectasis	2 (4%)		2 (4%)	1 (2%)
Atrophy	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Cyst	11 (22%)	12 (24%)	19 (39%)	16 (33%)
Degeneration, fatty				1 (2%)
Infiltration cellular, mast cell				1 (2%)
Inflammation	1 (2%)		1 (2%)	
Thrombosis	1 (2%)		2 (4%)	
Corpus luteum, hyperplasia				1 (2%)
Germinal epithelium, hyperplasia		1 (2%)	1 (2%)	
Interstitial cell, hyperplasia			1 (2%)	
Uterus	(50)	(50)	(49)	(50)
Adenomyosis				1 (2%)
Angiectasis	2 (4%)	3 (6%)	1 (2%)	
Hydrometra	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, cystic	2 (4%)		2 (4%)	6 (12%)
Inflammation	1 (2%)			
Lymphangiectasis			1 (2%)	
Thrombosis	1 (2%)			
Arteriole, hyperplasia				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis				1 (2%)
Hyperplasia	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Hyperplasia, megakaryocyte				1 (2%)
Lymph node	(4)	(7)	(6)	(1)
Angiectasis	1 (25%)	1 (14%)		
Hyperplasia	1 (25%)			
Iliac, hyperplasia	1 (25%)			
Pancreatic, hyperplasia		1 (14%)		
Lymph node, bronchial	(41)	(39)	(41)	(37)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia	1 (2%)	6 (15%)	4 (10%)	
Hyperplasia, histiocytic				1 (3%)
Lymph node, mandibular	(37)	(38)	(40)	(38)
Hyperplasia	1 (3%)	2 (5%)	2 (5%)	1 (3%)
Lymph node, mesenteric	(47)	(48)	(49)	(50)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Lymph node, mediastinal	(31)	(40)	(38)	(34)
Hyperplasia	2 (6%)	2 (5%)	5 (13%)	
Hyperplasia, lymphoid			1 (3%)	
Spleen	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation	24 (48%)	29 (58%)	32 (65%)	35 (70%)
Hyperplasia, lymphoid	6 (12%)	15 (30%)	12 (24%)	10 (20%)
Pigmentation, hemosiderin	39 (78%)	44 (88%)	46 (94%)	48 (96%)
Thymus	(46)	(41)	(46)	(48)
Atrophy	1 (2%)	2 (5%)		
Hyperplasia, lymphoid	1 (2%)	2 (5%)	1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Inflammation, chronic active	1 (2%)			
Necrosis		1 (2%)		
Pinna, inflammation, chronic	1 (2%)			
Subcutaneous tissue, edema	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Arthrosis				1 (2%)
Fibrous osteodystrophy	22 (44%)	28 (56%)	25 (50%)	21 (42%)
Maxilla, fracture	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Hemorrhage	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)		
Necrosis	1 (2%)			
Meninges, infiltration cellular, mononuclear cell	2 (4%)			2 (4%)
Respiratory System				
Larynx	(50)	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)	3 (6%)		1 (2%)
Squamous epithelium, hyperplasia	2 (4%)	8 (16%)	3 (6%)	5 (10%)
Lung	(50)	(50)	(50)	(50)
Hemorrhage	10 (20%)	2 (4%)	6 (12%)	6 (12%)
Infiltration cellular, histiocyte	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Inflammation		1 (2%)		
Metaplasia, osseous	1 (2%)			
Pigmentation, hemosiderin	1 (2%)			
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)		2 (4%)
Mediastinum, inflammation		1 (2%)		
Perivascular, inflammation	2 (4%)			
Nose	(50)	(50)	(49)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)		
Inflammation, suppurative	2 (4%)	3 (6%)	1 (2%)	
Olfactory epithelium, atrophy	2 (4%)	4 (8%)	2 (4%)	4 (8%)
Olfactory epithelium, degeneration, hyaline	6 (12%)	14 (28%)	11 (22%)	12 (24%)
Olfactory epithelium, metaplasia	1 (2%)	1 (2%)		
Respiratory epithelium, degeneration, hyaline	17 (34%)	35 (70%)	26 (53%)	23 (46%)
Special Senses System				
Eye	(1)			(4)
Degeneration				1 (25%)
Cornea, inflammation, chronic	1 (100%)			3 (75%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Glomerulosclerosis	7 (14%)	2 (4%)	8 (16%)	8 (16%)
Inflammation, chronic active		1 (2%)		
Metaplasia, osseous	1 (2%)	1 (2%)	3 (6%)	4 (8%)
Nephropathy	34 (68%)	39 (78%)	38 (78%)	33 (66%)
Pigmentation, hemosiderin	1 (2%)	1 (2%)		
Renal tubule, degeneration			1 (2%)	
Renal tubule, hyperplasia		1 (2%)		
Renal tubule, mineralization		1 (2%)		
Urinary bladder	(47)	(49)	(48)	(50)
Inflammation	1 (2%)	1 (2%)		

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). 2-Butoxyethanol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of 2-butoxyethanol. In the absence of toxicity, 10,000 μg/plate was selected as the high dose.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). 2-Butoxyethanol was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of three doses of 2-butoxyethanol. In the SCE test, the highest testable dose of 2-butoxyethanol, in the absence of S9, was limited by toxicity to 3,000 (Trial 1) or 3,500 μg/mL (Trial 2); with S9, no toxicity was observed and the high dose was limited to 5,000 μg/mL. In the Abs test, the high dose was limited to 5,000 μg/mL. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with 2-butoxyethanol in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing 2-butoxyethanol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with 2-butoxyethanol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no 2-butoxyethanol. Incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Since a significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as

a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with 2-butoxyethanol for 8.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with 2-butoxyethanol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: if cell cycle delay was anticipated, the incubation period was extended.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One or two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

RAT AND MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by 2-butoxyethanol exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Published toxicity information was used to select doses. Male F344/N rats and $B6C3F_1$ mice were injected intraperitoneally three times at 24-hour intervals with 2-butoxyethanol dissolved in phosphate-buffered saline; the total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of phosphate-buffered saline. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the final injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation.

In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

2-Butoxyethanol (100 to 10,000 μg/plate) did not induce mutations in any of the *S. typhimurium* strains tested (TA97, TA98, TA100, TA1535, and TA1537), with or without induced hamster or rat liver S9 (Table E1; Zeiger *et al.*, 1992). In tests for induction of chromosomal damage in CHO cells *in vitro*, 2-butoxyethanol induced cell cycle delay (an indication of cytotoxicity) but did not induce either SCEs (Table E2) or Abs (Table E3) with or without S9. In the Abs test without S9, a weakly positive response was obtained in the second trial at the highest dose tested (5,000 μg/mL), but this response was not reproduced in a third trial and the test results were concluded to be negative overall. Due to the cell cycle delay caused by 2-butoxyethanol in the trials conducted without S9, a delayed harvest was used to increase the number of cells available for analysis. *In vivo*, no induction of micronuclei was observed in PCEs in bone marrow of rats or mice treated with 2-butoxyethanol (Tables E4 and E5). Rats received up to 450 mg/kg 2-butoxyethanol three times at 24-hour intervals via intraperitoneal injection; two out of five rats administered 450 mg/kg dose died. Mice were treated by the same protocol. All mice receiving 550 mg/kg survived, whereas 100% mortality occurred in the 1,100 mg/kg dose groups.

TABLE E1
Mutagenicity of 2-Butoxyethanol in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b]					
		−S9	+ hamster S9		+rat S9		
			10%	30%	5%	10%	30%
TA100	0	164 ± 5.5	153 ± 9.5	161 ± 7.5		172 ± 6.1	111 ± 2.8
	100	156 ±11.6	157 ± 3.2	166 ± 3.2		155 ± 8.3	127 ± 12.1
	333	157 ± 7.1	161 ± 12.7	157 ± 17.5		167 ± 8.5	99 ± 5.0
	1,000	165 ± 17.0	156 ± 1.8	150 ± 1.5		169 ± 4.7	96 ± 3.7
	3,333	166 ± 2.6	151 ± 4.8	151 ± 13.3		156 ± 3.3	150 ± 2.3
	10,000	112 ± 7.8	132 ± 15.5	149 ± 12.1		142 ± 9.2	119 ± 4.0
Trial summary		Negative	Negative	Negative		Negative	Negative
Positive control[c]		428 ± 30.9	930 ± 56.0	731 ± 52.2		471 ± 17.0	621 ± 9.8
TA1535	0	30 ± 4.9	14 ± 0.9	14 ± 2.6		12 ± 0.3	13 ± 0.3
	100	39 ± 0.3	13 ± 0.6	12 ± 1.5		10 ± 4.7	14 ± 1.5
	333	33 ± 4.3	12 ± 1.8	14 ± 3.4		11 ± 1.3	14 ± 0.3
	1,000	25 ± 3.2	8 ± 1.8	12 ± 2.0		11 ± 0.7	12 ± 2.5
	3,333	25 ± 3.2	13 ± 4.0	12 ± 0.6		8 ± 0.9	10 ± 0.3
	10,000	22 ± 2.5	7 ± 2.5	10 ± 1.0		11 ± 0.6	10 ± 2.0
Trial summary		Negative	Negative	Negative		Negative	Negative
Positive control		585 ± 26.0	203 ± 10.1	698 ± 29.8		195 ± 16.0	186 ± 4.5
TA1537	0	11 ± 3.2		13 ± 1.5			13 ± 3.4
	100	13 ± 2.6		14 ± 2.1			11 ± 1.8
	333	13 ± 1.9		7 ± 1.2			8 ± 1.2
	1,000	10 ± 1.9		12 ± 1.5			9 ± 3.3
	3,333	9 ± 1.3		10 ± 2.3			12 ± 4.1
	10,000	14 ± 2.4		11 ± 1.3			7 ± 0.6
Trial summary		Negative		Negative			Negative
Positive control		742 ± 61.5		64 ± 3.8			49 ± 2.9
TA97	0	180 ± 15.1	171 ± 10.4	180 ± 3.0	183 ± 11.9	178 ± 6.6	198 ± 11.3
	100	178 ± 4.9	170 ± 18.0	210 ± 8.2	177 ± 8.9	195 ± 8.5	215 ± 13.2
	333	190 ± 8.4	169 ± 3.0	197 ± 5.2	187 ± 2.0	195 ± 16.5	210 ± 5.0
	666				154 ± 9.5	195 ± 15.1	170 ± 15.2
	1,000	214 ± 3.7	204 ± 6.9	193 ± 3.3	169 ± 10.3	184 ± 6.4	149 ± 11.4
	1,666				161 ± 19.1	166 ± 22.1	178 ± 2.9
	3,333	190 ± 2.7	172 ± 11.5	164 ± 0.7			
	10,000	181 ± 1.8	148 ± 10.3	130 ± 4.1			
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		799 ± 76.2	285 ± 14.7	465 ± 20.5	494 ± 22.3	355 ± 13.1	308 ± 8.8

TABLE E1
Mutagenicity of 2-Butoxyethanol in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate				
		-S9	+ hamster S9		+ rat S9	
			10%	30%	10%	30%
TA98	0	25 ± 2.3	19 ± 0.6	32 ± 1.9	34 ± 1.9	40 ± 0.6
	100	24 ± 3.0	26 ± 1.0	22 ± 3.4	33 ± 3.5	35 ± 4.7
	333	22 ± 2.5	20 ± 0.9	28 ± 2.0	22 ± 3.4	37 ± 5.7
	1,000	25 ± 5.0	27 ± 0.6	28 ± 0.9	24 ± 3.2	34 ± 1.2
	3,333	21 ± 2.8	26 ± 2.9	30 ± 1.2	27 ± 1.7	34 ± 2.3
	10,000	11 ± 1.5[d]	21 ± 4.3	27 ± 1.2	23 ± 2.8	42 ± 1.2
Trial summary		Negative	Negative	Negative	Negative	Negative
Positive control		488 ± 48.6	933 ± 29.6	528 ± 35.3	355 ± 7.4	135 ± 6.9

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Zeiger *et al*. (1992). 0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97 and TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.
[d] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 2-Butoxyethanol[a]

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
−S9								
Trial 1								
Summary: Equivocal								
Medium[c]		50	1,016	418	0.41	8.4	26.0	
Mitomycin-C[d]	0.001	50	1,017	568	0.55	11.4	26.0	35.75
	0.010	5	103	150	1.45	30.0	26.0	253.98
2-Butoxyethanol	1,510	50	1,004	410	0.40	8.2	31.0[e]	−0.74
	2,220	50	998	453	0.45	9.1	31.0[e]	10.33
	3,000	50	1,013	496	0.48	9.9	31.0[e]	19.01
					P=0.001[f]			
Trial 2								
Summary: Negative								
Medium		50	1,027	485	0.47	9.7	26.0	
Mitomycin-C	0.001	50	1,015	626	0.61	12.5	26.0	30.60
	0.010	5	102	202	1.98	40.4	26.0	319.36
2-Butoxyethanol	2,500	50	1,007	531	0.52	10.6	36.0[e]	11.66
	3,000	50	1,009	541	0.53	10.8	36.0[e]	13.54
	3,500	50	1,007	551	0.54	11.0	36.0[e]	15.86
					P=0.010			
+S9								
Summary: Negative								
Medium		50	1,006	491	0.48	9.8	26.0	
Cyclophosphamide[d]	0.4	50	1,038	705	0.67	14.1	26.0	39.16
	2.0	5	102	128	1.25	25.6	26.0	157.11
2-Butoxyethanol	500	50	1,019	485	0.47	9.7	26.0	−2.48
	1,670	50	1,015	479	0.47	9.6	26.0	−3.31
	5,000	50	1,026	497	0.48	9.9	26.0	−0.75
					P=0.563			

[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented by Galloway *et al*. (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Since 2-butoxyethanol induced a delay in the cell division cycle, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[f] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2-Butoxyethanol[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
-S9					
Trial 1					
Harvest time: 10.5 hours					
Summary: Negative					
Medium[b]		200	7	0.04	3.5
Mitomycin-C[c]	0.25	200	22	0.11	10.5
	0.75	25	14	0.56	36.0
2-Butoxyethanol	2,513	200	3	0.02	1.5
	3,750	200	2	0.01	1.0
	5,000	100	0	0.00	0.0
					P=0.991[d]
Trial 2					
Harvest time: 20.5 hours[e]					
Summary: Weakly positive					
Medium		100	0	0.00	0.0
Mitomycin-C[f]	0.05	25	22	0.88	36.0
	0.08	200	16	0.08	5.0
2-Butoxyethanol	2,513	100	4	0.04	3.0
	3,750	100	1	0.01	1.0
	5,000	100	8	0.08	7.0*
					P=0.007
Trial 3					
Harvest time: 20.7 hours[e]					
Summary: Negative					
Medium		100	1	0.01	1.0
Mitomycin-C	0.05	100	27	0.27	22.0
	0.08	25	15	0.60	40.0
2-Butoxyethanol	4,500	100	1	0.01	1.0
	4,700	100	3	0.03	3.0
	5,000	100	2	0.02	2.0
					P=0.215

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2-Butoxyethanol

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
+S9					
Harvest time: 12.5 hours					
Summary: Negative					
Medium		200	6	0.03	3.0
Cyclophosphamide[c]	7.5	200	20	0.10	8.0
	37.5	25	10	0.40	36.0
2-Butoxyethanol	2,513	100	1	0.01	1.0
	3,750	200	8	0.04	3.5
	5,000	200	6	0.03	3.0
					P=0.368

* Positive response (P≤0.05) versus the solvent control
[a] Study was performed at Litton Bionetics, Inc. The detailed protocol is presented by Galloway *et al*. (1987).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose
[e] Due to a significant 2-butoxyethanol-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to provide sufficient first-division metaphase cells at harvest.
[f] Based on the observed responses, the positive control doses were apparently switched at the time of dosing.

TABLE E4
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Rats Treated with 2-Butoxyethanol by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Rats with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Phosphate-buffered saline[c]		5	1.9 ± 0.2
Cyclophosphamide[d]	7.50	5	21.0 ± 0.4
2-Butoxyethanol	7.03	5	1.6 ± 0.3
	14.06	5	2.1 ± 0.8
	28.12	5	2.2 ± 0.3
	56.25	5	1.3 ± 0.3
	112.50	5	1.7 ± 0.3
	225.00	5	1.2 ± 0.2
	450.00	3	2.2 ± 0.6
			P=0.570[e]

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

TABLE E5
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with 2-Butoxyethanol Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Phosphate-buffered saline[c]		5	2.5 ± 0.2
Cyclophosphamide[d]	10.00	5	12.9 ± 1.3
2-Butoxyethanol	17.19	5	2.6 ± 0.9
	34.38	5	2.3 ± 0.3
	68.78	5	3.2 ± 0.9
	137.50	5	3.8 ± 0.8[e]
	275.00	5	3.7 ± 0.4
	550.00	5	2.8 ± 0.4
			P=0.236[f]

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al*. (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] P=0.05 (pairwise comparison to the solvent control, P≤0.004 required for significance)
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F
HEMATOLOGY
AND BONE MARROW CELLULARITY RESULTS

TABLE F1
Hematology Data for Rats in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Male						
n	10	10	10	10	10	10
Automated hematocrit (mL/dL)	45.5 ± 0.4	43.8 ± 0.7	45.1 ± 0.4	42.7 ± 0.5**	38.4 ± 0.4**	34.9 ± 0.3**
Manual hematocrit (%)	46.8 ± 0.5	45.8 ± 0.6	47.0 ± 0.4	44.5 ± 0.5**	41.1 ± 0.3**	37.3 ± 0.4**
Hemoglobin (g/dL)	15.5 ± 0.1	14.8 ± 0.3	15.4 ± 0.1	14.5 ± 0.2**	13.1 ± 0.1**	11.7 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.05 ± 0.08	8.71 ± 0.14*	8.91 ± 0.06	8.01 ± 0.08**	7.10 ± 0.07**	5.97 ± 0.05**
Reticulocytes ($10^6/\mu L$)	0.16 ± 0.02	0.17 ± 0.03	0.15 ± 0.02	0.30 ± 0.04**	0.48 ± 0.06**	0.68 ± 0.07**
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.01	0.04 ± 0.03	0.11 ± 0.03	0.17 ± 0.04**	0.20 ± 0.06*
Mean cell volume (fL)	50.4 ± 0.3	50.2 ± 0.2	50.7 ± 0.2	53.1 ± 0.2**	53.8 ± 0.3**	58.5 ± 0.3**
Mean cell hemoglobin (pg)	17.1 ± 0.1	17.0 ± 0.1	17.3 ± 0.1	18.1 ± 0.1**	18.4 ± 0.1**	19.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.9 ± 0.2	33.7 ± 0.2	34.2 ± 0.2	33.9 ± 0.1	34.1 ± 0.2	33.4 ± 0.1
Platelets ($10^3/\mu L$)	482.3 ± 20.4	487.6 ± 31.3	499.0 ± 26.7	469.1 ± 20.8	486.2 ± 21.9	533.9 ± 35.9
Leukocytes ($10^3/\mu L$)	6.70 ± 0.29	6.29 ± 0.38	6.13 ± 0.33	5.87 ± 0.24*	5.72 ± 0.36*	5.34 ± 0.17**
Segmented neutrophils ($10^3/\mu L$)	1.12 ± 0.09	1.08 ± 0.09	1.12 ± 0.08	1.04 ± 0.09	0.99 ± 0.23	1.32 ± 0.32
Lymphocytes ($10^3/\mu L$)	5.34 ± 0.26	4.99 ± 0.33	4.82 ± 0.28	4.72 ± 0.22	4.65 ± 0.20*	3.93 ± 0.42**
Monocytes ($10^3/\mu L$)	0.19 ± 0.04	0.19 ± 0.05	0.11 ± 0.03	0.08 ± 0.02*	0.06 ± 0.02**	0.08 ± 0.04*
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.03 ± 0.01	0.08 ± 0.03	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Female						
n	10	10	10	10	9	5
Automated hematocrit (mL/dL)	46.7 ± 0.3	44.7 ± 0.5**	43.6 ± 0.5**	40.5 ± 0.3**	37.4 ± 0.3**	31.9 ± 0.6**
Manual hematocrit (%)	48.5 ± 0.5	46.0 ± 0.5**	45.2 ± 0.5**	42.9 ± 0.4**	40.0 ± 0.3**	36.2 ± 0.6**
Hemoglobin (g/dL)	15.6 ± 0.1	15.0 ± 0.1**	14.6 ± 0.1**	13.6 ± 0.1**	12.5 ± 0.1**	10.5 ± 0.3**
Erythrocytes ($10^6/\mu L$)	8.48 ± 0.05	8.08 ± 0.07**	7.70 ± 0.08**	6.91 ± 0.05**	6.07 ± 0.04**	4.77 ± 0.15**
Reticulocytes ($10^6/\mu L$)	0.13 ± 0.02	0.10 ± 0.01	0.16 ± 0.02	0.26 ± 0.04*	0.34 ± 0.04**	0.40 ± 0.11**
Nucleated erythrocytes ($10^3/\mu L$)	0.04 ± 0.02	0.05 ± 0.02	0.12 ± 0.03*	0.18 ± 0.07	0.61 ± 0.24**	0.73 ± 0.27**
Mean cell volume (fL)	55.1 ± 0.3	55.3 ± 0.2	56.4 ± 0.2**	58.7 ± 0.2**	61.6 ± 0.2**	66.8 ± 0.9**
Mean cell hemoglobin (pg)	18.4 ± 0.1	18.6 ± 0.2	19.0 ± 0.0**	19.6 ± 0.1**	20.6 ± 0.1**	22.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.1	33.6 ± 0.3	33.6 ± 0.1	33.6 ± 0.2	33.4 ± 0.1	32.9 ± 0.2
Platelets ($10^3/\mu L$)	573.5 ± 19.5	576.1 ± 31.6	583.5 ± 13.3	657.0 ± 25.7*	611.6 ± 25.6	719.6 ± 52.9*
Leukocytes ($10^3/\mu L$)	6.58 ± 0.23	6.99 ± 0.40	7.26 ± 0.41	6.88 ± 0.23	7.64 ± 0.48	7.21 ± 0.45
Segmented neutrophils ($10^3/\mu L$)	1.17 ± 0.12	1.24 ± 0.15	1.25 ± 0.12	1.20 ± 0.13	1.24 ± 0.16	1.37 ± 0.22
Lymphocytes ($10^3/\mu L$)	5.15 ± 0.19	5.53 ± 0.31	5.75 ± 0.35	5.45 ± 0.26	6.19 ± 0.42	5.75 ± 0.27
Monocytes ($10^3/\mu L$)	0.18 ± 0.04[b]	0.17 ± 0.05	0.22 ± 0.05	0.18 ± 0.05	0.19 ± 0.04	0.06 ± 0.03
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.02

* Significantly different ($P \le 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F2
Hematology and Bone Marrow Cellularity Data for Rats in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Male				
Hematology				
n				
3 Months	9	9	9	9
6 Months	9	8	9	8
12 Months	8	0[b]	9	9
Automated hematocrit (mL/dL)				
3 Months	46.2 ± 0.3	48.5 ± 0.4	46.1 ± 0.4	43.5 ± 0.3**
6 Months	47.1 ± 0.3	46.5 ± 0.6	47.4 ± 0.7	44.3 ± 0.4**
12 Months	46.1 ± 0.3	—	44.4 ± 0.7**	41.4 ± 1.1**
Manual hematocrit (%)				
3 Months	44.9 ± 0.2	46.9 ± 0.5	44.8 ± 0.4	42.9 ± 0.5*
6 Months	47.2 ± 0.2	46.4 ± 0.5	47.2 ± 0.6	44.3 ± 0.7**
12 Months	47.8 ± 0.4	—	45.9 ± 0.8*	42.9 ± 1.2**
Hemoglobin (g/dL)				
3 Months	15.0 ± 0.1	15.5 ± 0.1	15.0 ± 0.1	14.2 ± 0.1**
6 Months	15.2 ± 0.1	15.1 ± 0.2	15.3 ± 0.2	14.4 ± 0.1**
12 Months	15.2 ± 0.0	—	14.7 ± 0.2**	13.4 ± 0.3**
Erythrocytes ($10^6/\mu L$)				
3 Months	8.99 ± 0.06	9.19 ± 0.06	8.84 ± 0.09	8.01 ± 0.06**
6 Months	9.02 ± 0.08	8.85 ± 0.10	9.05 ± 0.14	8.16 ± 0.07**
12 Months	8.88 ± 0.08	—	8.39 ± 0.15**	7.43 ± 0.20**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.12 ± 0.02	0.14 ± 0.01	0.14 ± 0.02	0.20 ± 0.01**
6 Months	0.08 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.14 ± 0.01**
12 Months	0.11 ± 0.03	—	0.13 ± 0.02	0.19 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)				
3 Months	0.01 ± 0.01	0.04 ± 0.03	0.02 ± 0.02	0.05 ± 0.02
6 Months	0.05 ± 0.02	0.00 ± 0.00*	0.01 ± 0.01	0.02 ± 0.01
12 Months	0.05 ± 0.02	—	0.15 ± 0.10	0.04 ± 0.03
Mean cell volume (fL)				
3 Months	51.3 ± 0.3	52.8 ± 0.1**	52.0 ± 0.2*	54.2 ± 0.3**
6 Months	52.3 ± 0.5	52.5 ± 0.2	52.4 ± 0.2	54.4 ± 0.2**
12 Months	52.0 ± 0.2	—	52.9 ± 0.3*	55.8 ± 0.2**
Mean cell hemoglobin (pg)				
3 Months	16.7 ± 0.1	16.9 ± 0.0	16.9 ± 0.1	17.7 ± 0.0**
6 Months	16.9 ± 0.1	17.1 ± 0.1*	16.9 ± 0.1	17.6 ± 0.1**
12 Months	17.1 ± 0.2	—	17.5 ± 0.1	18.1 ± 0.1**
Mean cell hemoglobin concentration (g/dL)				
3 Months	32.5 ± 0.1	32.0 ± 0.1*	32.4 ± 0.1	32.6 ± 0.1
6 Months	32.3 ± 0.3	32.5 ± 0.1	32.3 ± 0.1	32.4 ± 0.1
12 Months	33.0 ± 0.2	—	33.1 ± 0.2	32.5 ± 0.2
Platelets ($10^3/\mu L$)				
3 Months	477.7 ± 6.9	432.1 ± 15.7	486.2 ± 8.8	473.3 ± 10.6
6 Months	501.2 ± 11.1	572.4 ± 36.1	602.3 ± 71.8	597.6 ± 35.6
12 Months	762.6 ± 33.5	—	789.2 ± 21.8	748.8 ± 26.9
Leukocytes ($10^3/\mu L$)				
3 Months	5.98 ± 0.34	12.37 ± 0.26**	6.71 ± 0.33	6.40 ± 0.32
6 Months	6.69 ± 0.54	7.83 ± 0.62	7.61 ± 0.77	6.79 ± 0.29
12 Months	6.45 ± 0.24	—	6.54 ± 0.48	6.10 ± 0.53
Segmented neutrophils ($10^3/\mu L$)				
3 Months	1.78 ± 0.34	1.62 ± 0.26	1.09 ± 0.11*	1.23 ± 0.10
6 Months	1.93 ± 0.27	2.42 ± 0.68	2.33 ± 0.66	1.47 ± 0.16
12 Months	1.83 ± 0.23	—	1.58 ± 0.25	1.57 ± 0.40

TABLE F2
Hematology and Bone Marrow Cellularity Data for Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Male (continued)				
Hematology (continued)				
n				
3 Months	9	9	9	9
6 Months	9	8	9	8
12 Months	8	0	9	9
Lymphocytes ($10^3/\mu L$)				
3 Months	4.07 ± 0.17	10.51 ± 0.29**	5.47 ± 0.30	5.13 ± 0.26
6 Months		4.59 ± 0.30	5.24 ± 0.29	5.08 ± 0.34
5.18 ± 0.26				
12 Months	4.54 ± 0.18	—	4.88 ± 0.35	4.46 ± 0.19
Monocytes ($10^3/\mu L$)				
3 Months	0.10 ± 0.03	0.11 ± 0.04	0.06 ± 0.03	0.04 ± 0.01
6 Months	0.10 ± 0.05	0.10 ± 0.03	0.13 ± 0.02	0.11 ± 0.05
12 Months	0.00 ± 0.00	—	0.02 ± 0.02	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)				
3 Months	0.04 ± 0.02	0.13 ± 0.05	0.08 ± 0.02	0.03 ± 0.01
6 Months	0.07 ± 0.02	0.06 ± 0.03	0.07 ± 0.03	0.04 ± 0.02
12 Months	0.09 ± 0.02	—	0.07 ± 0.02	0.06 ± 0.02
Bone Marrow Cellularity				
n				
3 Months	9	0	9	9
6 Months	9	9	9	9
12 Months	9	0	9	9
Nucleated bone marrow cells (10^6/femur)				
3 Months	82.9 ± 3.1	—	82.5 ± 2.6	88.8 ± 3.7
6 Months	103.0 ± 3.0	102.8 ± 7.4	104.3 ± 4.7	110.6 ± 3.4
12 Months	111.5 ± 6.4	—	102.6 ± 3.3	128.1 ± 3.1
Myeloid/erythroid ratio				
3 Months	1.232 ± 0.056	—	1.063 ± 0.059	1.023 ± 0.062
6 Months	0.958 ± 0.042	1.122 ± 0.076	1.118 ± 0.101	0.826 ± 0.045
12 Months	1.107 ± 0.126	—	1.042 ± 0.058	0.720 ± 0.048**

TABLE F2
Hematology and Bone Marrow Cellularity Data for Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Female				
Hematology				
n				
3 Months	8	9	9	9
6 Months	9	9	9	9
12 Months	9	0	8	9
Automated hematocrit (mL/dL)				
3 Months	48.9 ± 0.2	47.3 ± 0.5**	44.9 ± 0.5**	43.0 ± 0.4**
6 Months	46.0 ± 0.4	41.1 ± 1.5*	42.2 ± 0.9**	40.0 ± 0.3**
12 Months	44.2 ± 0.3	—	43.7 ± 0.3	40.7 ± 0.4**
Manual hematocrit (%)				
3 Months	46.5 ± 0.5	46.1 ± 0.5	43.3 ± 0.5**	42.2 ± 0.5**
6 Months	45.8 ± 0.4	41.9 ± 1.4*	43.1 ± 0.9**	41.4 ± 0.3**
12 Months	45.4 ± 0.2	—	45.3 ± 0.3	42.3 ± 0.4**
Hemoglobin (g/dL)				
3 Months	15.5 ± 0.1	14.8 ± 0.2**	14.3 ± 0.2**	13.7 ± 0.1**
6 Months	15.2 ± 0.1	13.7 ± 0.5**	13.9 ± 0.3**	13.2 ± 0.1**
12 Months	14.9 ± 0.1	—	14.6 ± 0.1	13.5 ± 0.1**
Erythrocytes ($10^6/\mu L$)				
3 Months	8.52 ± 0.03	8.10 ± 0.10**	7.54 ± 0.08**	7.08 ± 0.05**
6 Months	8.40 ± 0.07	7.50 ± 0.25**	7.54 ± 0.15**	6.89 ± 0.05**
12 Months	7.81 ± 0.05	—	7.42 ± 0.06**	6.75 ± 0.05**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.13 ± 0.01	0.16 ± 0.02	0.18 ± 0.02	0.20 ± 0.02*
6 Months	0.06 ± 0.01	0.08 ± 0.01	0.12 ± 0.01**	0.17 ± 0.01**
12 Months	0.06 ± 0.01	—	0.11 ± 0.02*	0.12 ± 0.02**
Nucleated erythrocytes ($10^3/\mu L$)				
3 Months	0.10 ± 0.03	0.18 ± 0.02	0.09 ± 0.03	0.26 ± 0.05*
6 Months	0.05 ± 0.03	0.02 ± 0.02	0.03 ± 0.01	0.04 ± 0.02
12 Months	0.07 ± 0.02	—	0.05 ± 0.02	0.25 ± 0.08*
Mean cell volume (fL)				
3 Months	57.4 ± 0.2	58.3 ± 0.2**	59.6 ± 0.4**	60.7 ± 0.4**
6 Months	54.8 ± 0.3	54.8 ± 0.4	56.0 ± 0.3*	58.2 ± 0.2**
12 Months	56.8 ± 0.2	—	58.8 ± 0.3**	60.3 ± 0.3**
Mean cell hemoglobin (pg)				
3 Months	18.2 ± 0.0	18.3 ± 0.1	18.9 ± 0.1**	19.3 ± 0.1**
6 Months	18.1 ± 0.1	18.3 ± 0.1	18.4 ± 0.1	19.2 ± 0.1**
12 Months	19.1 ± 0.1	—	19.7 ± 0.1**	20.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)				
3 Months	31.7 ± 0.1	31.3 ± 0.2	31.8 ± 0.2	31.8 ± 0.2
6 Months	33.2 ± 0.2	33.4 ± 0.2	32.9 ± 0.1	33.1 ± 0.1
12 Months	33.7 ± 0.2	—	33.6 ± 0.2	33.2 ± 0.2
Platelets ($10^3/\mu L$)				
3 Months	556.4 ± 14.3	686.6 ± 78.4	591.7 ± 25.3	562.1 ± 25.7
6 Months	576.3 ± 9.4	563.0 ± 16.6	558.4 ± 18.8	591.9 ± 18.0
12 Months	663.3 ± 18.2	—	635.0 ± 12.5	702.3 ± 16.0
Leukocytes ($10^3/\mu L$)				
3 Months	7.20 ± 0.51	11.79 ± 1.02**	7.18 ± 0.43	7.17 ± 0.22
6 Months	6.27 ± 0.37	6.48 ± 0.33	6.03 ± 0.39	6.66 ± 0.29
12 Months	4.74 ± 0.30	—	4.31 ± 0.51	4.70 ± 0.17
Segmented neutrophils ($10^3/\mu L$)				
3 Months	1.44 ± 0.30	2.50 ± 0.88	1.19 ± 0.13	1.23 ± 0.08
6 Months	1.63 ± 0.41	1.38 ± 0.28	1.13 ± 0.10	1.26 ± 0.14
12 Months	1.07 ± 0.08	—	1.03 ± 0.12	1.00 ± 0.09

TABLE F2
Hematology and Bone Marrow Cellularity Data for Rats in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	31.2 ppm	62.5 ppm	125 ppm
Female (continued)				
Hematology (continued)				
n				
3 Months	8	9	9	9
6 Months	9	9	9	9
12 Months	9	0	8	9
Lymphocytes ($10^3/\mu L$)				
3 Months	5.61 ± 0.27	9.15 ± 0.34**	5.81 ± 0.32	5.82 ± 0.19
6 Months	4.32 ± 0.18	4.70 ± 0.35	4.65 ± 0.32	5.21 ± 0.22*
12 Months	3.63 ± 0.29	—	3.21 ± 0.39	3.67 ± 0.14
Monocytes ($10^3/\mu L$)				
3 Months	0.05 ± 0.03	0.02 ± 0.02	0.10 ± 0.04	0.04 ± 0.02
6 Months	0.23 ± 0.04	0.30 ± 0.04	0.16 ± 0.03	0.17 ± 0.03
12 Months	0.02 ± 0.01	—	0.01 ± 0.01	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)				
3 Months	0.09 ± 0.03	0.10 ± 0.03	0.08 ± 0.03	0.06 ± 0.02
6 Months	0.08 ± 0.02	0.08 ± 0.02	0.10 ± 0.04	0.02 ± 0.01
12 Months	0.03 ± 0.01	—	0.04 ± 0.01	0.04 ± 0.01
Bone Marrow Cellularity				
n				
3 Months		8	0	9
9				
6 Months	9	9	9	9
12 Months	9	0	8	9
Nucleated bone marrow cells (10^6/femur)				
3 Months	62.8 ± 4.4	—	68.4 ± 3.7	84.0 ± 2.0**
6 Months		63.6 ± 2.3	64.8 ± 4.8	64.0 ± 4.5
89.7 ± 2.4**				
12 Months	74.3 ± 4.8	—	81.8 ± 4.4	110.1 ± 5.6**
Myeloid/erythroid ratio				
3 Months	1.060 ± 0.084	—	0.840 ± 0.036	0.744 ± 0.044**
6 Months	1.137 ± 0.061	1.037 ± 0.066	0.788 ± 0.040**	0.708 ± 0.025**
12 Months	0.846 ± 0.047	—	0.766 ± 0.031	0.690 ± 0.046*

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] Not examined at this exposure concentration

TABLE F3
Hematology Data for Mice in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
n	10	10	10	10	10	6
Male						
Automated hematocrit (mL/dL)	47.7 ± 1.0	48.8 ± 0.4	48.0 ± 0.6	47.1 ± 0.5	44.2 ± 0.3**	35.1 ± 1.4**
Manual hematocrit (%)	47.3 ± 1.0	48.3 ± 0.4	47.6 ± 0.5	46.6 ± 0.4	44.2 ± 0.4**	36.3 ± 1.4**
Hemoglobin (g/dL)	15.7 ± 0.4	16.0 ± 0.1	15.9 ± 0.1	15.4 ± 0.1**	14.4 ± 0.1**	11.4 ± 0.4**
Erythrocytes ($10^6/\mu L$)	9.71 ± 0.22	10.04 ± 0.08	9.77 ± 0.10	9.47 ± 0.06*	8.90 ± 0.07**	7.21 ± 0.23**
Reticulocytes ($10^6/\mu L$)	0.21 ± 0.03	0.22 ± 0.03	0.21 ± 0.02	0.32 ± 0.03*	0.45 ± 0.04**	0.79 ± 0.20**
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	49.1 ± 0.4	48.5 ± 0.3	49.0 ± 0.4	49.7 ± 0.4	49.8 ± 0.4	48.3 ± 0.9
Mean cell hemoglobin (pg)	16.2 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	16.2 ± 0.0	16.2 ± 0.1	15.8 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.2	32.8 ± 0.3	33.0 ± 0.2	32.7 ± 0.2	32.5 ± 0.2	32.5 ± 0.3
Platelets ($10^3/\mu L$)	922.5 ± 29.9	878.0 ± 22.1	894.0 ± 23.7	933.5 ± 30.0	1,001.3 ± 46.4	1,176.7 ± 78.2*
Leukocytes ($10^3/\mu L$)	2.76 ± 0.27[b]	2.27 ± 0.21	2.04 ± 0.25	2.54 ± 0.19	1.91 ± 0.22	2.13 ± 0.26
Segmented neutrophils ($10^3/\mu L$)	0.41 ± 0.05[b]	0.30 ± 0.04	0.30 ± 0.05	0.39 ± 0.07	0.28 ± 0.07	0.18 ± 0.02*
Lymphocytes ($10^3/\mu L$)	2.32 ± 0.24[b]	1.94 ± 0.19	1.72 ± 0.24	2.12 ± 0.16	1.61 ± 0.17	1.94 ± 0.28
Monocytes ($10^3/\mu L$)	0.01 ± 0.00[b]	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01[b]	0.02 ± 0.01	0.01 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Female						
Automated hematocrit (mL/dL)	47.1 ± 0.4	46.6 ± 0.3	46.4 ± 0.3	45.4 ± 0.5*	42.0 ± 0.4**	35.8 ± 0.7**
Manual hematocrit (%)	46.2 ± 0.3	45.9 ± 0.3	45.8 ± 0.3	45.1 ± 0.2**	42.3 ± 0.4**	37.8 ± 1.0**
Hemoglobin (g/dL)	15.7 ± 0.1	15.4 ± 0.1*	15.4 ± 0.1*	14.8 ± 0.1**	13.7 ± 0.1**	11.6 ± 0.1**
Erythrocytes ($10^6/\mu L$)	9.72 ± 0.05	9.55 ± 0.06*	9.51 ± 0.06*	9.18 ± 0.05**	8.57 ± 0.06**	7.35 ± 0.07**
Reticulocytes ($10^6/\mu L$)	0.18 ± 0.02	0.21 ± 0.03	0.19 ± 0.02	0.29 ± 0.02**	0.47 ± 0.04**	1.17 ± 0.28**
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	48.3 ± 0.3	48.8 ± 0.2	48.8 ± 0.2	49.5 ± 0.5	49.0 ± 0.3	48.8 ± 1.0
Mean cell hemoglobin (pg)	16.1 ± 0.1	16.0 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	16.0 ± 0.0	15.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.3 ± 0.2	33.0 ± 0.3	33.2 ± 0.2	32.6 ± 0.2	32.6 ± 0.2	32.4 ± 0.4*
Platelets ($10^3/\mu L$)	838.0 ± 19.0	779.7 ± 29.5	854.7 ± 18.1	930.3 ± 44.1	1,032.1 ± 44.1**	1,179.0 ± 75.6**
Leukocytes ($10^3/\mu L$)	2.68 ± 0.18	2.77 ± 0.17	2.46 ± 0.09	2.48 ± 0.13	2.52 ± 0.10	3.10 ± 0.33
Segmented neutrophils ($10^3/\mu L$)	0.26 ± 0.04	0.28 ± 0.03	0.24 ± 0.05	0.23 ± 0.03	0.25 ± 0.04	0.35 ± 0.08
Lymphocytes ($10^3/\mu L$)	2.38 ± 0.16	2.46 ± 0.16	2.19 ± 0.09	2.21 ± 0.11	2.24 ± 0.11	2.71 ± 0.27
Monocytes ($10^3/\mu L$)	0.01 ± 0.00	0.01 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.02

* Significantly different ($P \le 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F4
Hematology and Bone Marrow Cellularity Data for Mice in the 2-Year Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male				
Hematology				
n				
3 Months	10	10	10	10
6 Months	10	10	10	10
12 Months	10	10	9	10
Automated hematocrit (mL/dL)				
3 Months	46.3 ± 0.4	46.3 ± 0.3	44.9 ± 0.5*	42.5 ± 0.2**
6 Months	48.1 ± 0.4	47.6 ± 0.5	46.6 ± 0.3*	43.4 ± 0.4**
12 Months	48.8 ± 0.5	50.1 ± 2.0	47.0 ± 1.0	42.4 ± 0.5**
Manual hematocrit (%)				
3 Months	47.5 ± 0.3	47.3 ± 0.5	46.0 ± 0.4*	43.7 ± 0.2**
6 Months	48.1 ± 0.4	48.1 ± 0.4	47.2 ± 0.4	44.5 ± 0.3**
12 Months	47.9 ± 0.4	48.7 ± 1.9	46.4 ± 1.0	42.1 ± 0.4**
Hemoglobin (g/dL)				
3 Months	15.2 ± 0.1	15.3 ± 0.1	14.7 ± 0.2	13.8 ± 0.1**
6 Months	15.7 ± 0.2	15.6 ± 0.1	15.2 ± 0.1**	14.3 ± 0.1**
12 Months	15.7 ± 0.1	16.0 ± 0.7	14.9 ± 0.4*	13.6 ± 0.2**
Erythrocytes ($10^6/\mu L$)				
3 Months	9.61 ± 0.22	9.83 ± 0.06	9.41 ± 0.11	8.95 ± 0.05**
6 Months	9.88 ± 0.10	9.79 ± 0.08	9.58 ± 0.07*	9.09 ± 0.07**
12 Months	9.58 ± 0.07	9.73 ± 0.49	9.36 ± 0.32*	8.33 ± 0.10**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.07 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.13 ± 0.01**
6 Months	0.05 ± 0.01	0.07 ± 0.01	0.09 ± 0.01**	0.17 ± 0.01**
12 Months	0.06 ± 0.02	0.06 ± 0.02	0.11 ± 0.02	0.07 ± 0.02
Mean cell volume (fL)				
3 Months	48.6 ± 1.2	47.1 ± 0.2	47.7 ± 0.2	47.4 ± 0.3
6 Months	48.8 ± 0.4	48.6 ± 0.3	48.6 ± 0.3	47.8 ± 0.2
12 Months	50.9 ± 0.3	51.7 ± 0.5	50.3 ± 0.8	51.1 ± 0.6
Mean cell hemoglobin (pg)				
3 Months	15.9 ± 0.4	15.5 ± 0.0	15.7 ± 0.0	15.4 ± 0.1
6 Months	15.9 ± 0.1	16.0 ± 0.1	15.9 ± 0.1	15.7 ± 0.1
12 Months	16.4 ± 0.1	16.5 ± 0.2	16.0 ± 0.3	16.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)				
3 Months	32.8 ± 0.1	33.0 ± 0.1	32.8 ± 0.1	32.4 ± 0.1
6 Months	32.6 ± 0.2	32.9 ± 0.2	32.7 ± 0.2	32.9 ± 0.2
12 Months	32.2 ± 0.2	32.0 ± 0.1	31.7 ± 0.3	31.9 ± 0.1
Platelets ($10^3/\mu L$)				
3 Months	904.2 ± 18.3	888.2 ± 11.7	869.8 ± 13.4	940.6 ± 18.9
6 Months	988.3 ± 16.8	955.4 ± 34.1	1,028.8 ± 20.6	1,075.2 ± 17.1**
12 Months	831.2 ± 38.1	997.6 ± 37.8**	1,116.6 ± 69.5**	1,112.8 ± 39.4**
Leukocytes ($10^3/\mu L$)				
3 Months	3.63 ± 0.41	3.99 ± 0.37	3.92 ± 0.33	4.01 ± 0.44
6 Months	2.35 ± 0.35	2.09 ± 0.24	2.69 ± 0.27	2.41 ± 0.26
12 Months	3.27 ± 0.17	3.19 ± 0.48	3.06 ± 0.26	2.98 ± 0.17
Segmented neutrophils ($10^3/\mu L$)				
3 Months	0.67 ± 0.11	0.73 ± 0.08	0.81 ± 0.09	0.95 ± 0.15
6 Months	0.43 ± 0.08	0.43 ± 0.04	0.75 ± 0.09*	0.62 ± 0.09
12 Months	0.80 ± 0.04	0.84 ± 0.12	0.80 ± 0.13	0.70 ± 0.08
Lymphocytes ($10^3/\mu L$)				
3 Months	2.89 ± 0.31	3.17 ± 0.29	3.05 ± 0.26	3.00 ± 0.32
6 Months	1.87 ± 0.28	1.63 ± 0.22	1.88 ± 0.19	1.72 ± 0.22
12 Months	2.45 ± 0.15	2.34 ± 0.38	2.23 ± 0.18	2.27 ± 0.14

TABLE F4
Hematology and Bone Marrow Cellularity Data for Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Male (continued)				
Hematology (continued)				
n				
3 Months	10	10	10	10
6 Months	10	10	10	10
12 Months	10	10	9	10
Monocytes ($10^3/\mu L$)				
3 Months	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
6 Months	0.05 ± 0.02	0.03 ± 0.01	0.06 ± 0.02	0.06 ± 0.02
12 Months	0.01 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)				
3 Months	0.07 ± 0.02	0.10 ± 0.02	0.04 ± 0.01	0.06 ± 0.02
6 Months	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
12 Months	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Bone Marrow Cellularity				
Nucleated bone marrow cells (10^6/femur)				
3 Months	23.4 ± 0.8	22.8 ± 0.6	22.1 ± 1.1	23.5 ± 0.9
6 Months	23.8 ± 0.9	23.3 ± 1.0	23.5 ± 1.2	24.3 ± 1.4
12 Months	32.9 ± 0.9	28.9 ± 0.9	30.1 ± 1.3	30.0 ± 1.5
Myeloid/erythroid ratio				
3 Months	1.99 ± 0.10	2.11 ± 0.10	1.98 ± 0.13	2.02 ± 0.06
6 Months	1.88 ± 0.08[b]	2.24 ± 0.10	2.33 ± 0.09**	2.10 ± 0.09
12 Months	1.78 ± 0.12	2.15 ± 0.07	2.34 ± 0.07**	2.06 ± 0.10

TABLE F4
Hematology and Bone Marrow Cellularity Data for Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Female				
Hematology				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	10	10
Automated hematocrit (mL/dL)				
3 Months	48.9 ± 0.5	48.2 ± 0.3	46.0 ± 0.4**	42.8 ± 0.4**
6 Months	48.2 ± 0.5	46.2 ± 0.6*	45.7 ± 0.3**	42.5 ± 0.3**
12 Months	47.4 ± 0.5	46.9 ± 0.5	43.7 ± 0.6**	42.4 ± 0.4**
Manual hematocrit (%)				
3 Months	49.3 ± 0.5	48.9 ± 0.4	46.2 ± 0.5**	43.7 ± 0.5**
6 Months	48.1 ± 0.6	46.6 ± 0.5*	45.7 ± 0.2**	42.8 ± 0.2**
12 Months	46.9 ± 0.4	46.3 ± 0.4	43.8 ± 0.4**	41.8 ± 0.3**
Hemoglobin (g/dL)				
3 Months	15.5 ± 0.2	15.3 ± 0.1	14.6 ± 0.1**	13.4 ± 0.3**
6 Months	15.6 ± 0.2	14.9 ± 0.2**	14.7 ± 0.1**	13.6 ± 0.1**
12 Months	15.4 ± 0.1	15.0 ± 0.1*	14.3 ± 0.1**	13.6 ± 0.1**
Erythrocytes ($10^6/\mu L$)				
3 Months	9.89 ± 0.09	9.68 ± 0.07	9.23 ± 0.09**	8.58 ± 0.07**
6 Months	9.71 ± 0.15	9.33 ± 0.12*	9.19 ± 0.06**	8.68 ± 0.05**
12 Months	9.32 ± 0.09	9.14 ± 0.08	8.50 ± 0.12**	8.08 ± 0.09**
Reticulocytes ($10^6/\mu L$)				
3 Months	0.05 ± 0.00	0.06 ± 0.01	0.09 ± 0.01**	0.16 ± 0.01**
6 Months	0.05 ± 0.01	0.06 ± 0.01	0.09 ± 0.01**	0.14 ± 0.01**
12 Months	0.10 ± 0.01	0.14 ± 0.02	0.15 ± 0.02	0.24 ± 0.03**
Mean cell volume (fL)				
3 Months	49.3 ± 0.3	49.7 ± 0.2	49.8 ± 0.3	49.8 ± 0.1
6 Months	49.8 ± 0.6	49.5 ± 0.3	49.8 ± 0.4	49.0 ± 0.3
12 Months	50.9 ± 0.3	51.3 ± 0.3	51.5 ± 0.2	52.4 ± 0.3**
Mean cell hemoglobin (pg)				
3 Months	15.7 ± 0.1	15.8 ± 0.0	15.8 ± 0.1	15.7 ± 0.1
6 Months	16.1 ± 0.2	16.0 ± 0.1	16.0 ± 0.1	15.7 ± 0.1
12 Months	16.6 ± 0.1	16.5 ± 0.1	16.8 ± 0.1	16.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)				
3 Months	31.8 ± 0.1	31.7 ± 0.1	31.7 ± 0.1	31.4 ± 0.1*
6 Months	32.4 ± 0.2	32.3 ± 0.2	32.1 ± 0.1	32.1 ± 0.1
12 Months	32.6 ± 0.2	32.2 ± 0.2	32.7 ± 0.2	32.0 ± 0.2
Platelets ($10^3/\mu L$)				
3 Months	835.8 ± 27.5	832.9 ± 26.9	849.9 ± 12.4	921.3 ± 23.3*
6 Months	938.6 ± 27.2	942.5 ± 34.9	1,010.6 ± 24.9*	1,064.6 ± 12.9**
12 Months	778.1 ± 28.2	837.6 ± 14.0*	844.5 ± 28.6**	952.9 ± 12.1**
Leukocytes ($10^3/\mu L$)				
3 Months	3.11 ± 0.16	2.79 ± 0.19	3.52 ± 0.19	4.10 ± 0.45
6 Months	3.04 ± 0.16	3.78 ± 0.39	3.62 ± 0.25	3.78 ± 0.36
12 Months	2.45 ± 0.22	2.74 ± 0.36	3.32 ± 0.22	3.12 ± 0.25
Segmented neutrophils ($10^3/\mu L$)				
3 Months	0.49 ± 0.11	0.38 ± 0.05	0.50 ± 0.07	0.59 ± 0.05
6 Months	0.50 ± 0.05	0.83 ± 0.25	1.05 ± 0.31*	0.74 ± 0.07
12 Months	0.56 ± 0.06	0.79 ± 0.14	0.75 ± 0.06*	0.88 ± 0.09**
Lymphocytes ($10^3/\mu L$)				
3 Months	2.57 ± 0.12	2.38 ± 0.16	2.96 ± 0.17	3.46 ± 0.40
6 Months	2.43 ± 0.15	2.84 ± 0.27	2.45 ± 0.25	2.94 ± 0.28
12 Months	1.87 ± 0.18	1.91 ± 0.24	2.46 ± 0.17	2.21 ± 0.18

TABLE F4
Hematology and Bone Marrow Cellularity Data for Mice in the 2-Year Inhalation Study of 2-Butoxyethanol

	Chamber Control	62.5 ppm	125 ppm	250 ppm
Female (continued)				
Hematology (continued)				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	10	10
Monocytes ($10^3/\mu$L)				
3 Months	0.00 ± 0.00	0.01 ± 0.00	0.01 ± 0.01*	0.00 ± 0.00
6 Months	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02
12 Months	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu$L)				
3 Months	0.06 ± 0.02	0.03 ± 0.01	0.05 ± 0.02	0.05 ± 0.02
6 Months	0.06 ± 0.02	0.05 ± 0.03	0.07 ± 0.02	0.06 ± 0.02
12 Months	0.03 ± 0.01	0.04 ± 0.01	0.10 ± 0.03	0.03 ± 0.02
Bone Marrow Cellularity				
n				
3 Months	10	10	10	9
6 Months	10	10	10	10
12 Months	10	10	9	10
Nucleated bone marrow cells (10^6/femur)				
3 Months	23.0 ± 0.9	22.7 ± 1.0	23.2 ± 0.7	22.9 ± 0.9
6 Months	26.5 ± 0.9	26.3 ± 1.6	24.6 ± 1.2	26.9 ± 0.5
12 Months	32.7 ± 1.0	31.0 ± 1.9	34.7 ± 1.0	35.8 ± 1.0
Myeloid/erythroid				
3 Months	1.72 ± 0.12	2.03 ± 0.10	2.19 ± 0.10*	1.52 ± 0.09[c]
6 Months	1.81 ± 0.06	1.94 ± 0.13	2.08 ± 0.07*	1.90 ± 0.07
12 Months	1.53 ± 0.10	1.98 ± 0.08*	1.94 ± 0.13	1.59 ± 0.11

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9
[c] n=10

APPENDIX G
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	363 ± 7	371 ± 6	375 ± 4	357 ± 9	355 ± 7	366 ± 6
Heart						
Absolute	1.033 ± 0.023	1.097 ± 0.030	1.030 ± 0.015	1.002 ± 0.020	1.028 ± 0.012	1.106 ± 0.016
Relative	2.84 ± 0.04	2.95 ± 0.04	2.75 ± 0.04	2.81 ± 0.04	2.90 ± 0.05	3.03 ± 0.04*
R. Kidney						
Absolute	1.210 ± 0.021	1.265 ± 0.035	1.242 ± 0.020	1.224 ± 0.032	1.265 ± 0.028	1.441 ± 0.029**
Relative	3.33 ± 0.03	3.40 ± 0.05	3.31 ± 0.05	3.43 ± 0.06	3.56 ± 0.07**	3.94 ± 0.05**
Liver						
Absolute	12.663 ± 0.304	13.243 ± 0.331[b]	13.529 ± 0.245	13.015 ± 0.378	14.665 ± 0.543**	16.428 ± 0.384**
Relative	34.86 ± 0.49	35.83 ± 0.56[b]	36.07 ± 0.67	36.45 ± 0.76	41.32 ± 1.46**	44.99 ± 1.03**
Lung						
Absolute	1.709 ± 0.046	1.901 ± 0.095	1.846 ± 0.064	1.746 ± 0.045	1.697 ± 0.046	1.637 ± 0.042
Relative	4.71 ± 0.10	5.10 ± 0.20	4.91 ± 0.14	4.90 ± 0.11	4.79 ± 0.14	4.48 ± 0.10
R. Testis						
Absolute	1.429 ± 0.017	1.455 ± 0.024	1.420 ± 0.014	1.397 ± 0.026	1.431 ± 0.022	1.383 ± 0.065
Relative	3.94 ± 0.08	3.92 ± 0.06	3.78 ± 0.02	3.92 ± 0.09	4.04 ± 0.07	3.81 ± 0.21
Thymus						
Absolute	0.323 ± 0.012	0.317 ± 0.011	0.337 ± 0.019	0.288 ± 0.013	0.292 ± 0.009	0.290 ± 0.011
Relative	0.89 ± 0.03	0.86 ± 0.03	0.90 ± 0.05	0.81 ± 0.03	0.82 ± 0.03	0.79 ± 0.03
Female						
n	10	10	10	10	9	5
Necropsy body wt	222 ± 5	216 ± 4	211 ± 4	214 ± 4	210 ± 7	201 ± 4*
Heart						
Absolute	0.715 ± 0.013	0.703 ± 0.011	0.715 ± 0.014	0.724 ± 0.010	0.731 ± 0.021	0.750 ± 0.009
Relative	3.22 ± 0.05	3.26 ± 0.05	3.39 ± 0.07*	3.39 ± 0.05*	3.49 ± 0.07**	3.73 ± 0.03**
R. Kidney						
Absolute	0.744 ± 0.023	0.750 ± 0.012	0.761 ± 0.017	0.818 ± 0.015**	0.821 ± 0.027**	0.908 ± 0.015**
Relative	3.35 ± 0.07	3.48 ± 0.06	3.61 ± 0.08**	3.83 ± 0.05**	3.91 ± 0.06**	4.51 ± 0.04**
Liver						
Absolute	7.111 ± 0.194	7.052 ± 0.168	7.100 ± 0.207	7.855 ± 0.188*	8.309 ± 0.336**	8.692 ± 0.147**
Relative	31.98 ± 0.53	32.71 ± 0.61	33.63 ± 0.65	36.73 ± 0.49**	39.58 ± 1.01**	43.22 ± 0.74**
Lung						
Absolute	1.232 ± 0.040	1.247 ± 0.059	1.185 ± 0.022	1.265 ± 0.039	1.217 ± 0.049	1.112 ± 0.019
Relative	5.55 ± 0.17	5.81 ± 0.33	5.62 ± 0.10	5.93 ± 0.19	5.79 ± 0.12	5.53 ± 0.12
Thymus						
Absolute	0.250 ± 0.008	0.249 ± 0.010	0.241 ± 0.011	0.246 ± 0.011	0.246 ± 0.009	0.187 ± 0.011**
Relative	1.13 ± 0.03	1.15 ± 0.03	1.14 ± 0.04	1.15 ± 0.04	1.18 ± 0.04	0.93 ± 0.06**

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Inhalation Study of 2-Butoxyethanol[a]

	Chamber Control	31 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
n	10	10	10	10	10	6
Male						
Necropsy body wt	37.6 ± 0.9	37.0 ± 0.7	38.1 ± 0.7	35.9 ± 0.8	35.2 ± 0.7*	33.3 ± 0.4**
Heart						
Absolute	0.167 ± 0.003	0.169 ± 0.005	0.176 ± 0.007	0.164 ± 0.005	0.173 ± 0.008	0.165 ± 0.004
Relative	4.45 ± 0.11	4.57 ± 0.12	4.62 ± 0.18	4.58 ± 0.14	4.93 ± 0.22	4.95 ± 0.09
R. Kidney						
Absolute	0.329 ± 0.007	0.314 ± 0.017	0.333 ± 0.009	0.314 ± 0.006	0.319 ± 0.008	0.315 ± 0.013
Relative	8.74 ± 0.21	8.50 ± 0.48	8.76 ± 0.27	8.77 ± 0.21	9.07 ± 0.15	9.45 ± 0.32
Liver						
Absolute	1.682 ± 0.044	1.603 ± 0.034	1.751 ± 0.053	1.684 ± 0.031	1.768 ± 0.050	1.838 ± 0.049*
Relative	44.77 ± 0.99	43.27 ± 0.43	45.97 ± 1.21	47.05 ± 1.24	50.28 ± 0.97**	55.20 ± 1.29**
Lung						
Absolute	0.236 ± 0.019	0.223 ± 0.003	0.233 ± 0.007	0.219 ± 0.006	0.222 ± 0.006	0.220 ± 0.007
Relative	6.28 ± 0.51	6.03 ± 0.09	6.12 ± 0.17	6.10 ± 0.10	6.32 ± 0.15	6.61 ± 0.22
R. Testis						
Absolute	0.113 ± 0.002	0.118 ± 0.003	0.114 ± 0.002	0.115 ± 0.002	0.115 ± 0.002	0.107 ± 0.007
Relative	3.02 ± 0.09	3.19 ± 0.05	2.99 ± 0.06	3.21 ± 0.05	3.28 ± 0.07	3.22 ± 0.22
Thymus						
Absolute	0.042 ± 0.003	0.041 ± 0.003	0.042 ± 0.003	0.039 ± 0.002	0.036 ± 0.002	0.037 ± 0.002
Relative	1.12 ± 0.08	1.11 ± 0.07	1.11 ± 0.08	1.10 ± 0.07	1.03 ± 0.06	1.12 ± 0.07
Female						
Necropsy body wt	31.3 ± 0.7	32.5 ± 0.9	31.4 ± 0.8	30.9 ± 0.7	31.0 ± 0.4	28.9 ± 0.8
Heart						
Absolute	0.135 ± 0.003	0.144 ± 0.004	0.141 ± 0.003	0.141 ± 0.003	0.135 ± 0.004	0.147 ± 0.002
Relative	4.32 ± 0.08	4.47 ± 0.17	4.51 ± 0.12	4.59 ± 0.12	4.36 ± 0.14	5.08 ± 0.12**
R. Kidney						
Absolute	0.220 ± 0.006	0.220 ± 0.006	0.224 ± 0.006	0.224 ± 0.003	0.220 ± 0.005	0.233 ± 0.011
Relative	7.07 ± 0.26	6.81 ± 0.21	7.18 ± 0.24	7.28 ± 0.14	7.09 ± 0.12	8.04 ± 0.22**
Liver						
Absolute	1.495 ± 0.050	1.557 ± 0.059	1.485 ± 0.052	1.539 ± 0.057	1.575 ± 0.045	1.620 ± 0.078
Relative	47.80 ± 1.21	48.12 ± 1.76	47.43 ± 1.29	49.93 ± 1.58	50.71 ± 0.93	55.89 ± 1.63**
Lung						
Absolute	0.213 ± 0.004	0.218 ± 0.003	0.218 ± 0.002	0.223 ± 0.004	0.217 ± 0.004	0.210 ± 0.007
Relative	6.83 ± 0.18	6.75 ± 0.16	6.98 ± 0.13	7.25 ± 0.15	7.00 ± 0.12	7.25 ± 0.08
Thymus						
Absolute	0.053 ± 0.002	0.055 ± 0.003	0.048 ± 0.002	0.051 ± 0.003	0.047 ± 0.003	0.051 ± 0.002
Relative	1.70 ± 0.05	1.70 ± 0.07	1.53 ± 0.06	1.65 ± 0.08	1.51 ± 0.08	1.77 ± 0.10

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX H
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF 2-BUTOXYETHANOL

2-Butoxyethanol was obtained from Dow Chemical U.S.A. (Plaquemine, LA) in two lots. Lot QP-911021-26D1 was used during the 14-week studies, and lot QP-921215-26D2 was used during the 2-year studies. Identity and purity analyses were conducted by the study laboratory. Reports on analyses performed in support of the 2-butoxyethanol studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a clear, colorless liquid, were identified as 2-butoxyethanol by infrared and nuclear magnetic resonance (proton and C^{13}) spectroscopy. The spectra were consistent with those expected for the structure, with the literature spectra (*Aldrich*, 1981, 1983), and/or with those of a reference sample obtained from Aldrich Chemical Company (Milwaukee, WI). The infrared and proton nuclear magnetic spectra are presented in Figures H1 and H2.

The purity of each lot was determined by elemental analysis (performed by Huffman Laboratories, Inc., Golden, CO, for lot QP-911021-26D1 and Galbraith Laboratories, Inc., Knoxville, TN, for lot QP-921215-26D2), Karl Fischer water analysis, titrations for acid and peroxide content, and gas chromatography. Free acid content was determined by titration with sodium hydroxide to the phenolphthalein endpoint. For the determination of peroxide content, samples were dissolved in sulfuric acid; molybdate solution and excess potassium iodide were then added, and the samples were allowed to sit in the dark for 15 minutes. Starch indicator was added, and the samples were titrated to the colorimetric endpoint with approximately 0.005 N sodium thiosulfate. Several gas chromatography systems were used to characterize the 2-butoxyethanol used in the 14-week and 2-year studies; the details of the systems are given in Table H1. Gas chromatography with flame ionization detection using system A was used for area percent analysis of the bulk chemical. Gas chromatography with flame ionization detection using system B (14-week studies) or system C (2-year studies) was used to determine percent purity relative to reference material. Additionally, the ethylene oxide content was measured with system B. Impurities in the bulk chemical were characterized using gas chromatography with mass spectrometry (system D).

For lot QP-911021-26D1, elemental analyses for carbon, hydrogen, and oxygen were in agreement with the theoretical values for 2-butoxyethanol. Karl Fischer water analysis indicated 0.02% water. Titrations indicated 0.001% acidity (as acetic acid) and 105 ppm peroxide, well within the acceptable limits of 0.02% acid and 5,000 ppm peroxide set for these studies. Gas chromatography indicated a major peak and one impurity with an area of 0.1% of the major peak area; less than 200 ppm ethylene oxide was detected. Concurrent analyses were performed on the reference material obtained from Aldrich Chemical Company. Results of elemental analyses were similar. The reference sample contained 0.12% water, 0.04% acetic acid, 5,537 ppm peroxide, and less than 200 ppm ethylene oxide; no impurities with areas of 0.1% or greater relative to the major peak area were detected by gas chromatography. Major peak comparisons of lot QP-911021-26D1 relative to the reference sample were performed by gas chromatography with flame ionization detection using system C with toluene as an internal standard and with a final temperature of 265° C; results indicated a purity of 100.8% for lot QP-911021-26D1 relative to the reference material. The overall purity of lot QP-911021-26D1 was determined to be greater than 99%.

For lot QP-921215-26D2, results of elemental analyses for carbon, hydrogen, and oxygen were in agreement with the theoretical values for 2-butoxyethanol. Karl Fischer water analysis indicated 0.0254% water. Titrations indicated less than 0.003% acetic acid and less than 1,000 ppm peroxide. Gas chromatography using system C indicated a major peak and three impurities with areas greater than 0.1% of

the major peak area. The ethylene oxide content was below the limit of detection (132 ppm). The reference material obtained from Aldrich Chemical Company and lot QP-911021-26D1 were analyzed concurrently with lot QP-921215-26D2 by gas chromatography. No impurities with areas of 0.1% or greater relative to the major peak area were detected in the reference sample; lot QP-911021-26D1 contained 0.12% ethylene glycol and approximately 0.03% 2-ethyl-2-hexenal. Major peak comparisons of lot QP-921215-26D2 relative to the reference sample were performed by gas chromatography as described for lot QP-911021-26D1; results indicated a purity of greater than 99.2% for lot QP-921215-26D2 relative to the reference sample. Three impurities with areas greater than 0.1% relative to the major peak area were identified in lot QP-921215-26D2; these impurities were tentatively identified with gas chromatography/ mass spectrometry using system D as ethylene glycol (0.10%), 2-ethyl-2-hexenal (0.19%), and 2-ethyl-1-hexanol (0.11%) coeluting with 2-(2-ethoxyethoxy)ethanol. The overall purity of lot QP-921215-26D2 was determined to be greater than 99%.

Accelerated stability studies of the bulk chemical were performed by Midwest Research Institute (MRI, Kansas City, MO) on a lot of 2-butoxyethanol not used in the current studies (MRI, 1984). Samples were analyzed by gas chromatography with flame ionization detection, a 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, a nitrogen carrier gas at a flow rate of 70 mL/minute, and an oven temperature of 130° C. n-Decane was added as an internal standard. These studies indicated that 2-butoxyethanol is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature during the 14-week studies and at approximately 16° C during the 2-year studies in stainless steel containers. Throughout the studies, stability was monitored by titrations for acid and peroxide and by gas chromatography with flame ionization detection by both area percent and relative purity methods. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

A diagram of the vapor generation and delivery system is shown in Figure H3. 2-Butoxyethanol was held in a stainless steel reservoir under a nitrogen blanket. A liquid micrometering pump was used to pump 2-butoxyethanol into a glass column filled with glass beads and heated by flexible electric heat tape encircling the column. Heated nitrogen entered the column from below, vaporized the 2-butoxyethanol, and carried it to a condenser column that was used to control generated vapor concentration. 2-Butoxyethanol that was not vaporized by the incoming heated nitrogen was collected along with any lower-boiling impurities in a flask below the glass-bead-filled column. Vapor temperature was monitored at the top of the condenser column by a temperature sensor. The total output of the generator was calculated from the metered nitrogen flow and the 2-butoxyethanol vapor pressure at the exit temperature.

To prevent 2-butoxyethanol from condensing while in transport to the exposure room, the Teflon® transport line was heated. The vapor was mixed with heated, HEPA- and charcoal-filtered air before entering a short vapor distribution manifold. An automatic controller maintained a constant flow in the distribution manifold.

From the distribution manifold, individual temperature-controlled Teflon® delivery lines carried the vapor to the exposure chambers. Flow to each chamber was produced by compressed-air pumps located at the chamber end of each delivery line. A three-way valve between the distribution line and each chamber directed vapor to the exposure chamber exhaust until a stable concentration of 2-butoxyethanol vapor collected in the distribution line. At each chamber, the vapor was further diluted with conditioned, filtered chamber air to the appropriate 2-butoxyethanol concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that 2-butoxyethanol vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

Chamber concentrations of 2-butoxyethanol were monitored with on-line gas chromatography/flame ionization detection using system E (14-week studies) or system F (2-year studies) (Table H1). A 12-port stream select valve coupled the on-line gas chromatograph and the exposure chambers. Each chamber was sampled approximately every 16 minutes (14-week studies) or every 30 minutes (2-year studies). The on-line gas chromatograph was checked daily for drift against an on-line standard of 2-butoxyethanol in nitrogen; the standard was prepared with a diffusion tube generator (Model 360, Thermo Electron, Hopkinton, MA). The on-line gas chromatograph was calibrated by comparing chamber concentration data to data collected from grab samples, which were collected with water-filled bubblers. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. Grab samples were analyzed by an off-line gas chromatograph with flame ionization detection (system G), which was calibrated using gravimetrically prepared standards of 2-butoxyethanol in water. No significant impurities were detected thus demonstrating the purity of the 2-butoxyethanol vapor in the exposure chambers reflected the purity of the starting material. Summaries of the chamber concentrations for the 14-week and 2-year studies are in Tables H2 and H3.

CHAMBER ATMOSPHERE CHARACTERIZATION

The theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes at a chamber airflow rate of 15 air changes per hour. Prior to and during the 14-week and 2-year studies, T_{90} and T_{10} ranges were determined with and without animals. The T_{90} values ranged from 8 to 12 minutes without animals and from 9 to 28 minutes with animals. The T_{10} values ranged from 8 to 14 minutes without animals and from 10 to 19 minutes with animals. A T_{90} value of 12 minutes was selected for all studies.

The uniformity of vapor concentration in the inhalation exposure chambers without animals was evaluated before each of the studies began; concentration uniformity with animals present in the chambers was also measured once during the 14-week studies and periodically during the 2-year studies. Vapor concentration was determined with the on-line gas chromatograph, with the 12-port sampling valve disabled to allow continuous monitoring from a single line; samples were taken from several positions in each chamber. Chamber concentration uniformity was maintained throughout the 14-week and 2-year studies.

The persistence of 2-butoxyethanol in the chamber following exposure was determined by monitoring the concentration overnight in the 500 ppm chamber in the 14-week studies, the 125 ppm chamber in the 2-year rat study, and the 250 ppm chamber in the 2-year mouse study, with and without animals present. In the 14-week studies, the concentration decreased to 1% of the target concentration within 54 minutes. In the 2-year rat study, the concentration decreased to 1% of the target concentration within 195 minutes with animals present and within 29 minutes without animals. In the 2-year mouse study, the concentration decreased to 1% of the target concentration within 36 minutes with animals present and within 26 minutes without animals. The increase in decay time in the 2-year rat study was attributed to the presence of rats in the chambers and not to residual 2-butoxyethanol in the monitoring system.

Before and during all studies, 2-butoxyethanol from the vapor generator reservoir, collection flask, distribution line, and chambers was tested for stability with gas chromatography using a 2-butoxyethanol standard as a reference. Results indicated that 2-butoxyethanol was stable in the reservoir for up to 21 days. 2-Butoxyethanol vapor was analyzed for volatile contaminants, peroxide, and acetic acid.

Before and during the 14-week studies, samples from the 0, 31, and 500 ppm exposure chambers were analyzed for ethylene oxide by the on-line gas chromatograph. Gas bag standards of ethylene oxide were volumetrically prepared and analyzed; ethylene oxide in the standards was detected at concentrations as low as 0.6 ppm. No ethylene oxide was detected in any exposure chamber; the concentration in the exposure chambers was estimated to be less than 0.1% (0.7 ppm). One to four impurities with a combined area of less than 0.03% (prestudy testing) or 0.1% relative to the major peak area were detected in the 500 ppm chamber by the on-line gas chromatograph. No impurities were found in the 31 ppm chamber. Samples were also collected from the 0, 31, and 500 ppm chambers and the vapor distribution line in solid-phase adsorbent glass sampling tubes. Each tube consisted of a front and a rear portion packed with adsorbent (ORBO Supelpak 20F). Any 2-butoxyethanol that escaped from the front portion was collected in the rear portion; samples were desorbed in 1 mL methanol before analysis using system A. Percent breakthrough was calculated as the ratio of the amount collected on the rear portion to the amount collected on the front portion. A breakthrough of 10% or less (prestudy testing) or 35% or less was observed for all chamber samples. Ethylene glycol was present as an impurity at 2% or less by weight; additional impurities were also observed with areas of up to 0.1% of the major peak area. These impurities were observed at similar concentrations in the bulk chemical. Samples were also collected from the 0, 31, and 500 ppm chambers and distribution line in acetonitrile-filled bubblers and analyzed for impurities and degradation products by gas chromatography/mass spectrometry using system D with an initial temperature of 50° C. These samples were analyzed against gravimetrically prepared standards of ethylene glycol, 1-butanol, 2-methyl-2-propanol (prestudy testing only), diethyleneglycol, 2-(2-ethoxy ethoxy) ethanol (prestudy testing only), and 2-(2-butoxy ethoxy) ethanol (14-week studies only) in acetonitrile. Samples of the bulk chemical were analyzed concomitantly. Results indicated that 1-butanol, diethylene glycol, 2-(2-ethoxy ethoxy) ethanol, and 2-(2-butoxy ethoxy) ethanol concentrations were less than 0.2%; ethylene glycol was detected in all samples collected during the studies. Additional impurities, tentatively identified as a branched alkane, 2-ethyl-2-hexenal, 2-ethyl-1-hexenol, and 2-ethyl-2-hexen-1-ol, were detected, and the concentrations were estimated to be less than 0.2% in one or more samples during prestudy testing and during the 14-week studies.

Before the 2-year studies, samples from the reservoir, condensation flask, distribution line, and exposure chambers were collected with acetonitrile-filled glass bubblers and analyzed by gas chromatography/mass spectrometry using system D for identity and gas chromatography with flame ionization detection using systems B and H for area percent. Samples of the bulk chemical were also analyzed. Additional samples collected with solid-phase sampling tubes were extracted with methanol and analyzed by gas chromatography with flame ionization detection using system H. Distribution line and exposure chamber samples contained impurities which were tentatively identified as 1-(2-methoxyethoxy) butane and 2-ethyl-2-hexenal. These impurities and ethylene glycol, 2-ethylhexanal, 2-ethyl-1-hexanol, 2-(2-ethoxyethoxy) ethanol, and 2-(2-butoxyethoxy) ethanol were identified in the reservoir and collection flask; 2-ethyl-2-hexen-1-ol was also tentatively identified. The concentrations of impurities which were previously identified in the bulk chemical did not increase from that determined in the bulk chemical. The concentration of 2-ethyl-2-hexenal was approximately 0.13% in the collection flask and approximately 0.25% in all other samples. Ethylene glycol was also detected in the collection flask at a concentration of 0.21% and in the reservoir at a concentration of 0.13%. The concentration of 2-ethyl-1-hexanol in the collection flask was 0.16%. The concentrations of all other impurities were 0.1% or less. During the 2-year studies, bubbler samples and sorbent tube samples were collected from the exposure system and analyzed by gas chromatography with flame ionization detection using systems C (for bubblers, with modified temperature program) and H (for sorbent tube samples). The most concentrated impurity was

2-ethyl-2-hexenal (approximately 0.25%); *n*-butanol, ethylene glycol, 2-ethylhexanal, 2-ethyl-1-hexanol, 2-(2-ethoxyethoxy) ethanol, and 1-(2-methoxyethoxy) butane were detected at concentrations of 0.1% or less. The concentrations of peroxide, ethylene oxide, and acetic acid in the reservoir and collection flask were analyzed before and during the 2-year studies as described for the bulk chemical analyses; concentrations were well below the maximum allowable concentrations. Ethylene oxide concentrations were also measured in samples from the distribution line and exposure chambers. Samples were collected with adsorbent tubes (ORBO-78, Supelco) containing a hydrogen bromide-impregnated sorbent that derived 2-bromoethanol from ethylene oxide. The primary and secondary beds of the sampling tube were mixed with sodium carbonate and extracted with a 50:50 solution of acetonitrile and toluene. Gas bag standards were prepared with ethylene oxide in methylene chloride. The samples were analyzed for 2-bromoethanol by gas chromatography with electron capture detection (system I). Ethylene oxide concentrations were less than 0.06% in the exposure chambers and distribution line. In all studies, the concentration of each impurity, relative to 2-butoxyethanol, detected in all distribution line and exposure chamber samples was the same as that detected in the reservoir, indicating that the impurities were neither concentrated nor dispersed by the generation system.

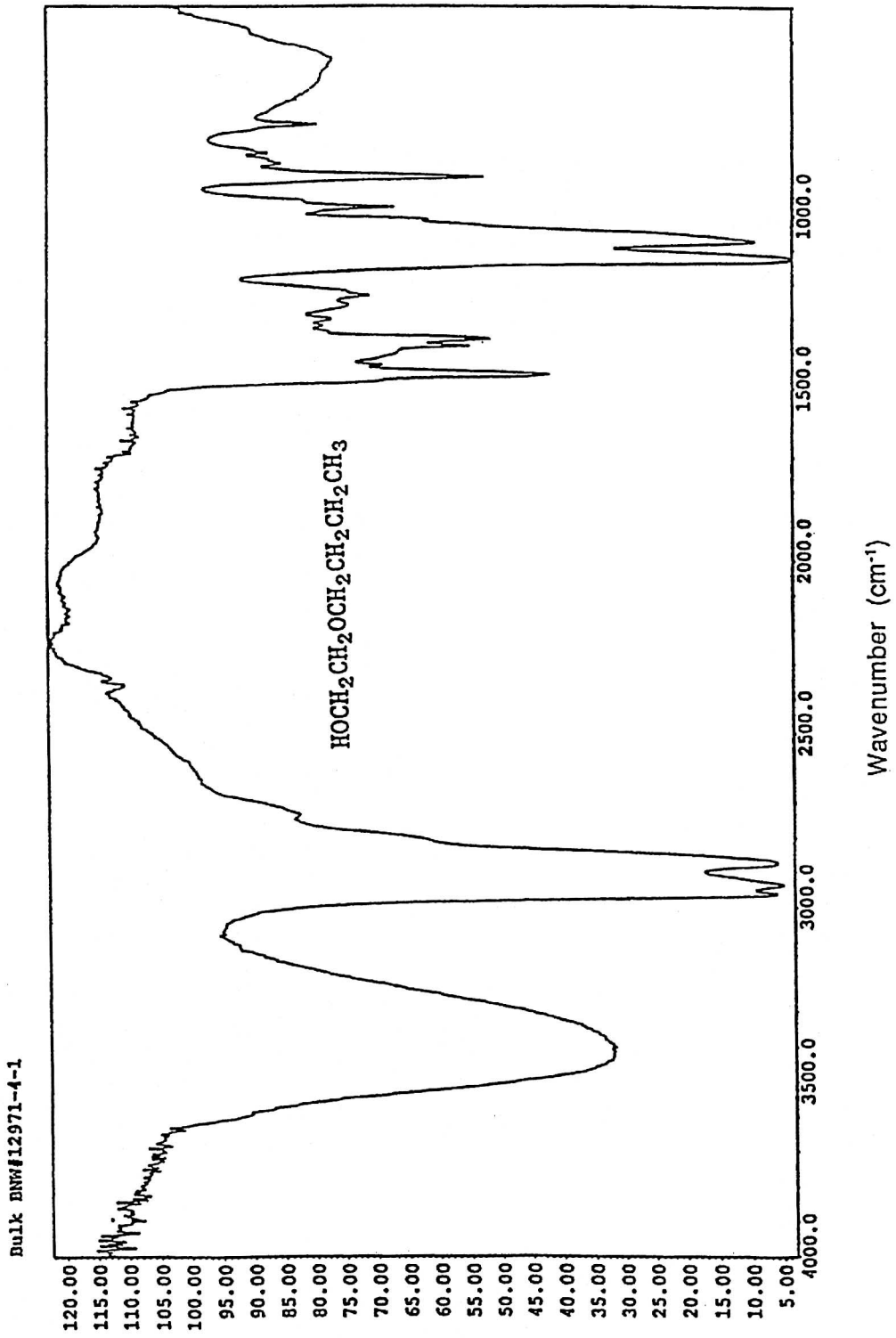

FIGURE H1
Growth Curves for Male and Female Mice
Exposed to 2-Butoxyethanol by Inhalation for 2 Years

FIGURE H2
Nuclear Magnetic Resonance Spectrum of 2-Butoxyethanol

TABLE H1
Gas Chromatography Systems Used in the 14-Week and 2-Year Inhalation Studies of 2-Butoxyethanol[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	DB WAX, 30 m × 0.53 mm, 1 μm film (J&W Scientific, Folsom, CA)	Helium at 11 mL/minute	30° C for 5 minutes, then 5° C/minute to 130° C, then 10° C/minute to 230° C, held for 5 minutes
System B			
Flame ionization	DB-1701, 60 m × 0.32 mm, 1 μm film (J&W Scientific)	Helium at 1.1 mL/minute	60° C for 4 minutes, then 12° C/minute to 250° C
System C			
Flame ionization	DB-1701, 60 m × 0.25 mm, 1 μm film (J&W Scientific)	Helium at 2.4 mL/minute	60° C for 4 minutes, then 12° C/minute to 265° C, held for 5 minutes
System D			
Mass spectrometry with electron impact ionization (29 to 200 amu)	Rtx-1701, 30 m × 0.25 mm, 1 μm film (Restek, Bellefonte, PA)	Helium at 6 psi head pressure	80° C for 5 minutes, then 5° C/minute to 250° C, held for 1 minute (cool-on-column injection)
System E			
Flame ionization	DB-1701, 15 m × 0.53 mm, 1 μm film (J&W Scientific)	Nitrogen at 20 mL/minute	Isothermal at 110° C
System F			
Flame ionization	Rtx-200, 30 m × 0.53 mm, 3 μm film (Restek)	Nitrogen at 50 mL/minute	Isothermal at 125° C
System G			
Flame ionization	DB WAX, 15 m × 0.53 mm, 1 μm film (J&W Scientific)	Helium at 15 mL/minute	95° C for 0.5 minutes, then 20° C/minute to 165° C (14-week studies) or 20° C/minute to 180° C (2-year studies)
System H			
Flame ionization	Rtx-200, 30 m × 0.53 mm, 3 μm film (Restek)	Helium at 6 psi head pressure	55° C for 0.5 minutes, then 5° C/minute to 100° C, held for 0.1 minutes, then 20° C/ minute to 250° C, held for 2 minutes (cool-on-column injection)
System I			
Electron capture	DB WAX, 30 m × 0.53 mm, 1 μm film (J&W Scientific)	Nitrogen at 9 mL/minute	Isothermal at 150° C

[a] All gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA).

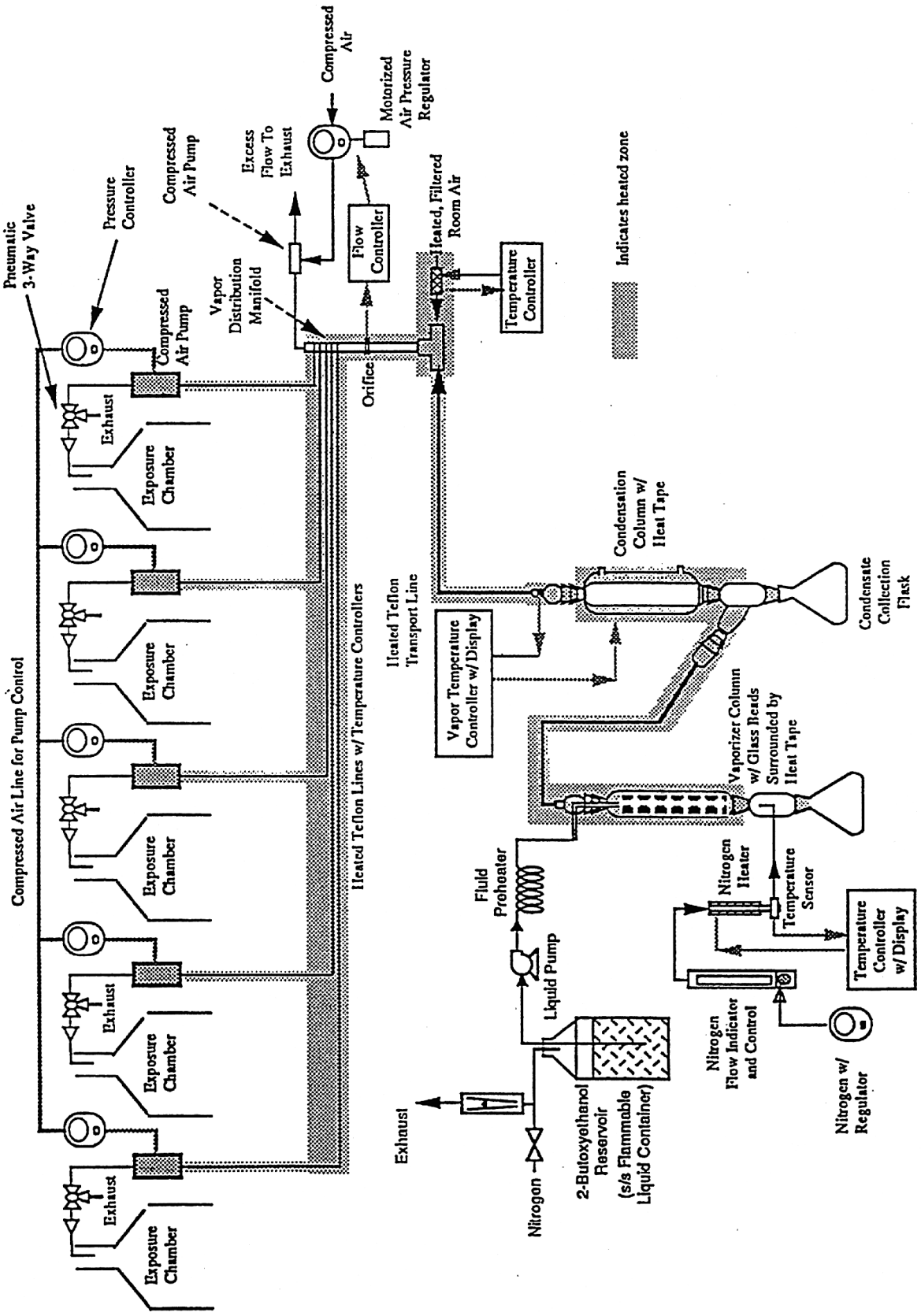

FIGURE H3
Schematic of the Vapor Generation and Delivery System in the 14-Week and 2-Year Inhalation Studies of 2-Butoxyethanol

TABLE H2
Summary of Chamber Concentrations in the 14-Week Inhalation Studies of 2-Butoxyethanol

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
31	1,387	31.0 ± 1.2
62.5	1,386	62.1 ± 1.8
125	1,385	125 ± 5.9
250	1,388	249 ± 11
500	1,413	497 ± 19
Mouse Chambers		
31	1,431	31.0 ± 1.2
62.5	1,430	62.1 ± 1.8
125	1,429	125 ± 5.8
250	1,432	249 ± 11
500	1,457	497 ± 19

[a] Mean ± standard deviation

TABLE H3
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of 2-Butoxyethanol

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
31.2	5,717	30.8 ± 1.8
62.5	5,728	62.3 ± 4.7
125	5,399	125.0 ± 7.8
Mouse Chambers		
62.5	5,403	62.7 ± 3.7
125	5,402	125 ± 8.1
250	5,362	248 ± 18.7

[a] Mean ± standard deviation

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

TABLE I1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE I2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.95 ± 0.49	22.1 – 23.6	23
Crude fat (% by weight)	5.39 ± 0.19	5.00 – 5.80	23
Crude fiber (% by weight)	3.12 ± 0.37	2.60 – 4.30	23
Ash (% by weight)	6.24 ± 0.15	5.72 – 6.54	23
Amino Acids (% of total diet)			
Arginine	1.273 ± 0.083	1.100 – 1.390	12
Cystine	0.307 ± 0.068	0.181 – 0.400	12
Glycine	1.152 ± 0.051	1.060 – 1.220	12
Histidine	0.581 ± 0.029	0.531 – 0.630	12
Isoleucine	0.913 ± 0.034	0.867 – 0.965	12
Leucine	1.969 ± 0.053	1.850 – 2.040	12
Lysine	1.269 ± 0.050	1.200 – 1.370	12
Methionine	0.436 ± 0.104	0.306 – 0.699	12
Phenylalanine	0.999 ± 0.114	0.665 – 1.110	12
Threonine	0.899 ± 0.059	0.824 – 0.985	12
Tryptophan	0.216 ± 0.146	0.107 – 0.671	12
Tyrosine	0.690 ± 0.091	0.564 – 0.794	12
Valine	1.079 ± 0.057	0.962 – 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.223	1.830 – 2.570	11
Linolenic	0.273 ± 0.034	0.210 – 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,657 ± 338	5,500 – 7,260	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5 – 48.9	12
Thiamine (ppm)	17.54 ± 3.70	14.0 – 26.0	22
Riboflavin (ppm)	7.78 ± 0.899	6.10 – 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0 – 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0 – 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60 – 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80 – 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190 – 0.354	12
Vitamin B_{12}	41.6 ± 18.6	10.6 – 65.0	12
Choline (ppm)	2,955 ± 382	2,300 – 3,430	11
Minerals			
Calcium (%)	1.16 ± 0.06	1.03 – 1.27	23
Phosphorus (%)	0.89 ± 0.03	0.84 – 0.97	23
Potassium (%)	0.886 ± 0.059	0.772 – 0.971	10
Chloride (%)	0.531 ± 0.082	0.380 – 0.635	10
Sodium (%)	0.316 ± 0.031	0.258 – 0.370	12
Magnesium (%)	0.165 ± 0.010	0.148 – 0.180	12
Sulfur (%)	0.266 ± 0.060	0.208 – 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0 – 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7 – 102.0	12
Zinc (ppm)	59.42 ± 9.73	46.1 – 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09 – 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52 – 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60 – 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49 – 1.23	8

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.53 ± 0.17	0.10 – 0.80	23
Cadmium (ppm)	0.05 ± 0.02	0.04 – 0.13	23
Lead (ppm)	0.23 ± 0.06	0.20 – 0.40	23
Mercury (ppm)[c]	<0.02		23
Selenium (ppm)	0.34 ± 0.10	0.10 – 0.50	23
Aflatoxins (ppb)	<5.0		23
Nitrate nitrogen (ppm)[d]	7.28 ± 2.45	2.90 – 11.0	23
Nitrite nitrogen (ppm)[d]	1.45 ± 0.91	0.30 – 3.50	23
BHA (ppm)[e]	1.07 ± 0.95	0.01 – 5.0	23
BHT (ppm)[e]	1.73 ± 1.17	0.18 – 5.0	23
Aerobic plate count (CFU/g)	128,000 ± 127,186	11,000 – 460,000	23
Coliform (MPN/g)	155 ± 582	3 – 2,800	23
Escherichia coli (MPN/g)	7 ± 3.5	3 – 10	23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[f]	12.20 ± 3.90	4.0 – 23.0	23
N-Nitrosodimethylamine (ppb)[f]	10.55 ± 3.64	3.0 – 21.0	23
N-Nitrosopyrrolidine (ppb)[f]	1.66 ± 0.56	1.0 – 2.9	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC[e]	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.13 ± 0.17	0.02 – 0.83	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

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

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 14-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
M. arthritidis	Study termination
Hemagglutination Inhibition	
H-1	6, 12, and 18 months, study termination
KRV	6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
14-Week Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
MHV (mouse hepatitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Ectromelia virus	6 months
EDIM	Study termination
Mouse adenoma virus-FL	12 months and study termination
M. arthritidis	Study termination
PVM	12 months
Sendai	Study termination
MCMV (mouse cytomegalovirus)	Study termination
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

RESULTS

All test results were negative.

APPENDIX K
H-*RAS* CODON 61 MUTATION SPECTRA IN FORESTOMACH NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO 2-BUTOXYETHANOL FOR 2 YEARS

Robert C. Sills, T. Ton, H. Lily Hong, Joe Roycroft, and Theodora R. Devereux
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

H-*RAS* CODON 61 MUTATION SPECTRA IN FORESTOMACH NEOPLASMS FROM B6C3F$_1$ MICE EXPOSED TO 2-BUTOXYETHANOL FOR 2 YEARS

INTRODUCTION

Various routes of chemical administration including oral, gavage, and inhalation may induce high incidences of forestomach neoplasms in rodent carcinogenicity bioassays. The mechanism of many of these forestomach carcinogens is unknown. The objective of this research is to investigate the effects of inhalation exposure in contributing to genetic alterations in cancer related genes, and to examine the factors underlying susceptibility of the forestomach to tumorigenesis. To date, there are no published data on the mutation spectrum and frequency of *ras* mutations in both spontaneous and chemical-induced forestomach neoplasms of B6C3F$_1$ mice.

Forestomach neoplasms occur in B6C3F$_1$ mice with a typical incidence of 0% to 2% in chamber control males and 0% to 3% in chamber control females in 2-year inhalation studies. Molecular analysis of rodent neoplasms for genetic alterations in cancer genes, such as the *ras* proto-oncogene, provides additional mechanistic information to help distinguish spontaneous neoplasms from chemical-induced neoplasms. For example, chemical-induced neoplasms in mice may have a high frequency of proto-oncogene activation, particularly by point mutations in codons 12, 13, and 61 of H- or K-*ras* genes (Devereux *et al.*, 1991; Sills *et al.*, 1995; Hong *et al.*, 1997). The frequency of *ras* activation in these neoplasms is often greater than that detected in neoplasms occurring in control animals, and there is evidence for chemical specificity in the pattern of mutations. The specific types of oncogene-activating mutations induced by a chemical carcinogen often agree with what is expected based on the DNA adducts formed by the agent. Even for "nongenotoxic carcinogens," patterns of *ras* gene mutations in neoplasms can give clues about the mechanism of tumorigenesis (Devereux *et al.*, 1993; Maronpot *et al.*, 1995).

MATERIALS AND METHODS

Forestomach Neoplasms: Male and female B6C3F$_1$ mice were exposed to 0, 62.5, 125, or 250 ppm 2-butoxyethanol by inhalation for 6 hours per day, 5 days per week for 2 years. At necropsy, forestomach neoplasms were fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin, sectioned to a thickness of 5 μm, and stained with hematoxylin and eosin. Subsequently, six unstained serial sections (10 μm thick) were prepared from paraffin blocks containing forestomach papillomas or carcinomas for isolation of DNA for polymerase chain reaction (PCR)-based assays. In order to isolate adequate amounts of DNA, forestomach neoplasms greater that 1 mm in diameter were identified for analysis. A total of 25 paraffin-embedded neoplasms was examined for genetic alterations in the H- and K-*ras* genes. This included 14 neoplasms from 2-butoxyethanol-exposed mice and 11 neoplasms from control mice from various NTP studies. Also, 14 forestomach neoplasms from mice exposed to 1,3-butadiene were evaluated for H- and K-*ras* mutations.

DNA Isolation: The DNA isolation procedure is described by Marmur (1961) and Sills *et al.* (1995). The paraffin-embedded tissue was deparaffinized and rehydrated before digestion with proteinase K (Wright and Manos, 1990). DNA was extracted with phenol and chloroform and precipitated with ethanol. DNA was quantified by optical density at 260 nm and 200 ng/μL was used for amplification.

DNA Amplification: DNA was amplified by PCR (Saiki *et al.*, 1988; Sills *et al.*, 1995); details of the use of nested primers are described by Devereux *et al.* (1991, 1993).

Restriction Fragment Length Polymorphic Identification: For identification of H-*ras* mutations at codon 61, restriction fragment length polymorphism (RFLP) was used, and most of exon 2 surrounding codon 61 was amplified (Sukumuar and Barbacid, 1990). The sense primer used for amplification of exon 2 was 5′-GACATCTTAGACACAGCAGTT-3′. A restriction site for MSE I, XbaI, or TaqI enzyme (New England Biolaboratory, Beverly, MA) is created by the presence of a C to A, A to T, or A to G mutation, respectively, in the first or second base of codon 61. By using this technique, one can detect codon 61 AAA, CTA, and CGA mutations by MSEI, XbaI and TaqI digestion, respectively; the normal sequence (CAA) of codon 61 is not cut by these enzymes. The reaction was incubated at 37° C (for MSEI or XbaI) or 60° C (for Taq I) for 2 hours. Fifteen μL of the mixture with bromophenol blue dye was loaded onto the 6% acrylamide TBE gel (8 × 8 cm × 1 mm; 15 wells) (Novex, San Diego, CA). The gel was run at 100 volts for 1 hour on the Novex gel electrophoresis unit. Gels were stained with a 5 μg/mL solution of ethidium bromide for 20 minutes and then destained in distilled water. Ethidium bromide-stained bands were visualized using a 312 nm ultraviolet viewing box and were photographed.

Single-Strand Conformation Polymorphism Analysis (*SSCP*): Single-strand conformation analysis (Orita *et al.*, 1989) was performed with PCR products into which [α-^{33}P]dATP was incorporated during the inner amplification. For the first exon of K-*ras*, 10% acrylamide gel containing 10% glycerol and 1X tris-borate-EDTA buffer was electrophoresed at room temperature with constant power at 8 watts for 16 hours on a Model S2 sequencing gel electrophoresis apparatus (Bethesda Research Labs, Gaithersburg, MD). For the second exon of H-*ras*, 12% acrylamide gel with 5% glycerol in 1X tris-borate-EDTA buffer was used at 35 watts in a 4° C cold room for 5 hours.

Direct Sequencing: Direct sequencing of the amplified second exon of the K-*ras* gene was performed as described by Tindall and Stankowski (1989) using previously described sequencing primers (Devereux *et al.*, 1991).

RESULTS

In order to determine if the 2-butoxyethanol-induced neoplasms contained an H-*ras* mutation profile similar to that observed with "spontaneous" neoplasms, sample groups of 12 and two neoplasms consisting of adenomas and carcinomas respectively, from various exposure groups, and 11 spontaneous neoplasms from the chamber controls (various studies), were evaluated by PCR amplification of H-*ras* exon 2 followed by RFLP analysis for codon 61 mutations in the B6C3F$_1$ mouse (Table K1). SSCP was used as an alternative screening method for detection of H- or K-*ras* mutations in DNA and mutations were confirmed by direct sequencing. A similar frequency (57%, 8/14) of H-*ras* mutations was detected in forestomach neoplasms when compared to the frequency (45%, 5/11) detected in spontaneous forestomach neoplasms from B6C3F$_1$ mice (Table K1). In addition, the primary H-*ras* mutation in forestomach neoplasms from the 2-butoxyethanol study and spontaneous neoplasms was a CGA mutation. There were no differences in the mutation frequency and spectrum between exposure groups (Table K1) or between benign and malignant forestomach neoplasms (data not shown). H-*ras* exon 1 or K-*ras* exon 1 and 2 mutations were not detected in forestomach neoplasms following exposure to 2-butoxyethanol.

Compared to the 2-butoxyethanol study, the mutation frequency detected in 1,3-butadiene forestomach neoplasms was 38% (9/24) (Table K1), which included 6 chemical-specific CTA codon 61 H-*ras* mutations, and three spontaneous CGA mutations.

DISCUSSION

In order to gain insight into the mechanism of 2-butoxyethanol induced forestomach carcinogenesis, H-*ras* oncogene mutation spectra in forestomach neoplasms from male and female $B6C3F_1$ mice exposed to 2-butoxyethanol for 2 years were compared. Codon 61 mutations in the H-*ras* gene were detected in 57% of the forestomach neoplasms induced by exposure to 2-butoxyethanol and 45% of the spontaneous neoplasms examined. In addition, the mutation profile within these chemical-induced forestomach neoplasms did not differ significantly from that in spontaneous neoplasms. This is the first study which demonstrates that the formation of both chemical-induced and spontaneous forestomach neoplasms in $B6C3F_1$ mice is associated with activation of the H-*ras* gene. The high frequency of activated H-*ras* genes detected in spontaneous forestomach neoplasms suggests that this gene is important in neoplasm formation in the $B6C3F_1$ mouse.

Results from this study suggests that the activation of the H-*ras* gene in the 2-butoxyethanol-induced forestomach neoplasms is not directly related to chemical exposure. Our findings indicate that 2-butoxyethanol may act in the forestomach to promote clonal growth of forestomach cells which were initiated spontaneously and which primarily contain an activated H-*ras* gene.

The similar mutation frequency and spectra of H-*ras* mutations detected in 2-butoxyethanol and spontaneous forestomach neoplasms is consistent with that seen with nongenotoxic agents in other organ systems (Devereux *et al.*, 1993; Maronpot *et al.*, 1995). Nongenotoxic agents by definition are not positive in *in vitro* assays and, therefore, the parent chemical or metabolites do not react with the DNA directly to cause mutations (Green, 1991). The findings of a similar frequency of *ras* mutations at codon 61 are consistent with the lack of mutagenicity in the *Salmonella typhimurium* assay and are consistent with the hypothesis that 2-butoxyethanol may be acting as a nongenotoxic carcinogen. In addition, the finding of no increase in the frequency of micronucleated erythrocytes in peripheral blood samples supports this theory.

Unlike the 2-butoxyethanol forestomach study, the finding of six H-*ras* codon 61 CTA mutations in 1,3-butadiene forestomach neoplasms and no CTA mutations in spontaneous forestomach neoplasms suggest that this is a chemical-specific mutation, consistent with the genotoxic properties of 1,3-butadiene (Melnick and Huff, 1992; Melnick and Kohn, 1995).

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TABLE K1
Patterns of H-*ras* Mutations in Forestomach Neoplasms from B6C3F$_1$ Mice

Treatment	Activated H-*ras* (%)	Codon 61 (Normal = CAA) CTA	CGA
Control[a]	5/11 (45)	0	5
2-Butoxyethanol[b]	8/14 (57)	0	8
1,3-Butadiene[c]	9/24 (38)	6	3

[a] Study controls combined with historical spontaneous forestomach neoplasms of control B6C3F$_1$ mice

b

[b] Male and female B6C3F$_1$ mice were exposed to 62.5, 125, or 250 ppm 2-butoxyethanol by inhalation for 6 hours per day, 5 days per week for 2 years.

[c] Male and female B6C3F$_1$ mice were exposed to 6.25 to 625 ppm 1,3-butadiene by inhalation for 2 years.