NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 378

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZALDEHYDE

(CAS NO. 100-52-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZALDEHYDE

(CAS NO. 100-52-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

Jack Bishop, Ph.D., Study Scientist

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

March 1990

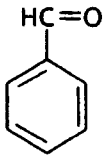
NTP TR 378

NIH Publication No. 90-2833

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

CONTENTS

APPENDIXES



BENZALDEHYDE

CAS No. 100-52-7

C_7H_6O Molecular weight 106.1

Synonyms: Artificial almond oil; artificial essential oil of almond; benzenecarbonal; benzene carbaldehyde; benzoic aldehyde; phenylmethanal

ABSTRACT

Benzaldehyde is an aromatic aldehyde used in the food, beverage, pharmaceutical, perfume, soap, and dyestuff industries. Toxicology and carcinogenesis studies were conducted by administering benzaldehyde (99% pure) in corn oil by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, Chinese hamster ovary (CHO) cells, and *Drosophila melanogaster*.

Sixteen-Day Studies: All rats that received 1,600 mg/kg died by day 2, and 2/5 males and 2/5 females that received 800 mg/kg died before the end of the studies. Final mean body weights of dosed and vehicle control rats were similar, with the exception of the 800 mg/kg groups, in which males were 14% lighter and females were 11% lighter than vehicle controls. All mice that received 1,600 or 3,200 mg/kg died by day 3. Final mean body weights of dosed and vehicle control mice were similar. No gross lesions attributable to benzaldehyde were detected upon necropsy.

Thirteen-Week Studies: Six of 10 male rats and 3/10 female rats that received 800 mg/kg and 1/10 female rats that received 400 mg/kg died near the end of the studies. Final mean body weights of dosed and vehicle control rats were similar, with the exception of male rats receiving 800 mg/kg, which were 26% lighter than vehicle controls. Compound-related lesions seen in rats receiving 800 mg/kg, but not in those receiving 400 mg/kg, included degeneration and necrosis in the cerebellum, necrosis in the hippocampus, hyperplasia and/or hyperkeratosis in the forestomach, and degeneration or necrosis of the liver and of the tubular epithelium in the kidney.

Nine of 10 male mice and 1/10 female mice that received 1,200 mg/kg benzaldehyde died by the end of the first week. Compound-related renal tubule degeneration and/or necrosis and reduction in final body weight were observed in the 600 mg/kg group of male mice. No reductions in body weight or compound-related lesions were seen in female mice.

Based on observations of compound-related lesions involving the brain, forestomach, kidney, and liver of male and female rats and the kidney of male mice in the 13-week studies, 2-year studies were conducted by administering 0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 103 weeks to groups of 50 male and 50 female rats and for 104 weeks to groups of 50 male mice. Based on survival data from the 16-day and 13-week studies, groups of 50 female mice were administered 0, 300, or 600 mg/kg benzaldehyde for 103 weeks.

Body Weights and Survival in the Two-Year Studies: Mean body weights of dosed rats and mice were similar to their respective vehicle controls throughout the studies. The survival of the high dose

group of male rats was lower than that of the vehicle controls after 1 year; no other significant differences were observed between any groups of rats or mice (survival--male rats: vehicle control, 37/50; low dose, 29/50; high dose, 21/50; female rats: 33/50; 33/50; 29/50; male mice: 32/50; 33/50; 31/50; female mice: 30/50; 27/50; 35/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: The only effects of benzaldehyde were those seen in the forestomach of mice. The incidences of uncommonly occurring squamous cell papillomas of the forestomach in both exposure groups were significantly greater than those in vehicle controls (male: vehicle control, 1/50; low dose, 2/50; high dose, 5/50; female: 0/50; 5/50; 6/50). The increased incidences of papillomas were accompanied by dose-related increases in the incidences in forestomach hyperplasia (male: 7/50; 8/50; 16/50; female: 12/50; 23/50; 39/50).

Genetic Toxicology: Benzaldehyde was not mutagenic in six strains of *S. typhimurium* and did not induce chromosomal aberrations in CHO cells, with or without exogenous metabolic activation. Benzaldehyde induced increases in trifluorothymidine-resistant mouse lymphoma cells in the absence of exogenous metabolic activation and increased sister chromatid exchanges in CHO cells in both the presence and absence of metabolic activation. Sex-linked recessive lethal mutations were not induced in the germ cells of adult male *D. melanogaster* administered benzaldehyde by feeding or by injection.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg per day. There was *some evidence of carcinogenic activity* of benzaldehyde for male or female $B6C3F_1$ mice, as indicated by increased incidences of squamous cell papillomas and hyperplasia of the forestomach. Female rats and male and female mice might have been able to tolerate higher doses.

---

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

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 200, or 400 mg/kg benzaldehyde in corn oil, 5 d/wk	0, 200, or 400 mg/kg benzaldehyde in corn oil, 5 d/wk	0, 200, or 400 mg/kg benzaldehyde in corn oil, 5 d/wk	0, 300, or 600 mg/kg benzaldehyde in corn oil, 5 d/wk
Body weights in the 2-year study			
Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar
Survival rates in the 2-year study			
37/50; 29/50; 21/50	33/50; 33/50; 29/50	32/50; 33/50; 31/50	30/50; 27/50; 35/50
Nonneoplastic effects			
None	None	Forestomach hyperplasia (7/50; 8/50; 16/50)	Forestomach hyperplasia (12/50; 23/50; 39/50)
Neoplastic effects			
None	None	Forestomach papillomas (1/50; 2/50; 5/50)	Forestomach papillomas (0/50; 5/50; 6/50)
Level of evidence of carcinogenic activity			
No evidence	No evidence	Some evidence	Some evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzaldehyde is based on 13-week studies that began in April 1981 and ended in June 1981 and on 2-year studies that began in January 1982 and ended in January 1984 at Southern Research Institute (Birmingham, AL).

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

Jack Bishop, Ph.D., Study Scientist

John R. Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.

(Discipline Leaders and Principal Contributors)

Douglas W. Bristol, Ph.D.
R. Chhabra, Ph.D.
R. Griesemer, D.V.M., Ph.D.
C.W. Jameson, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Douglas Walters, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 5/12/88)

John Seely, D.V.M. (Chair) (PATHCO, Inc.)
W. Ray Brown, D.V.M., Ph.D. (Research Pathology Service, Inc.)
Michael Elwell, D.V.M., Ph.D. (NTP)
James Heath, D.V.M. (Southern Research Institute)
Micheal Jokinen, D.V.M. (NTP)
Katsuhiko Yoshitomi, D.V.M., Ph.D. Experimental Pathology Laboratories, Inc.

(Evaluated Slides and Prepared Pathology Report for Mice on 5/1/87)

Robert Kovatch, D.V.M. (Chair) (Pathology Associates, Inc.)
Gary Burger, D.V.M. (R.J. Reynolds Co.)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Hershell Giles, D.V.M., Ph.D. (Southern Research Institute)
Nancy Gillet, D.V.M. (LITRI)
Robert Hruby, D.V.M. (Austrian Research Center, Seibersdorf)
Micheal Jokinen, D.V.M. (NTP)
Margarita McDonald, D.V.M., Ph.D. (NTP)
Kevin Morgan, B.V.Sc., M.R.C.V.S., Ph.D. Chemical Industry Institute of Toxicology

Principal Contributors at Southern Research Institute
(Conducted Studies and Evaluated Tissues)

J.D. Prejean, Ph.D.
Hershell Giles, D.V.M., Ph.D.
Ruby James, B.S.
James Heath, D.V.M.

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Provided Pathology Quality Assurance)

Micheal Jokinen, D.V.M.
Katsuhiko Yoshitomi, D.V.M., Ph.D.

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

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.
Naomi Levy, B.A.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on benzaldehyde on June 27, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D. (Chair)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, NJ

Ad Hoc Subcommittee Panel of Experts

John Ashby, Ph.D. (Principal Reviewer)
Imperial Chemical Industries, PLC
Central Toxicology Laboratory
Alderley Park, England

Robert H. Garman, D.V.M. (Principal Reviewer)
Bushy Run Laboratories
Export, PA
Consultants in Veterinary Pathology
Murrysville, PA

Lois Swirsky Gold, Ph.D.
University of California
Lawrence Berkeley Laboratory
Berkeley, CA

Curtis D. Klaassen, Ph.D.
Professor, Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

William Lijinsky, Ph.D.
Director, Chemical Carcinogenesis
Frederick Cancer Research Facility
Frederick, MD

Barbara McKnight, Ph.D.
Assistant Professor, Department of Biostatistics, University of Washington
Seattle, WA

Franklin E. Mirer, Ph.D. (Principal Reviewer)
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, MI

Paul M. Newberne, D.V.M., Ph.D.*
Professor, Mallory Institute of Pathology
Boston, MA

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZALDEHYDE

On June 27, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of benzaldehyde received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.B. Bishop, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female F344/N rats, some evidence of carcinogenic activity for male or female B6C3F$_1$ mice).

Dr. Garman, a principal reviewer, agreed with the conclusions. He appreciated the inclusion of tables comparing the genetic toxicity and the incidences of forestomach neoplasms with those observed in other pertinent NTP studies. He asked for a more detailed description of the brain lesions seen in high dose rats in the 13-week study; Dr. Bishop agreed (see page 27).

Dr. Ashby, the second principal reviewer, agreed with the conclusions. He noted that the conclusion of some evidence of carcinogenic activity in male mice was based on the dose-response trend and the dose-related increase in hyperplasia. Dr. Ashby spoke to the question of whether irritation leads to hyperplasia, which in turn leads to tumors. Dr. J. Huff, NIEHS, indicated that this has been a long-standing speculation and that the literature and NTP studies are replete with exceptions; for instance, the benzaldehyde studies in mice showed little evidence of forestomach irritation.

Dr. Mirer, the third principal reviewer, agreed with the conclusions in female rats and male mice. He said that the conclusion in male rats should be some evidence of carcinogenic activity or, at a minimum, equivocal evidence, based on increased incidences of pancreatic acinal cell adenomas with a significant trend and a significant pairwise comparison in the high dose group by the logistic regression test. Dr. Bishop noted that some of the highest incidences of pancreatic adenomas observed in NTP studies were found in several vehicle control groups from this study laboratory. This circumstance, along with only a marginal increase at the high dose (which was well within the historical control range), supported a conclusion of no evidence. Dr. Mirer argued that the studies provide clear evidence in female mice, if studies by the NTP or others can be shown to demonstrate progression of squamous papillomas of the forestomach to malignancy. Dr. S. Eustis, NIEHS, responded that there were no carcinomas to provide evidence of progression and that there was only a marginal increase in papillomas. Finally, Dr. Mirer stated that the results indicate that female rats and mice of each sex could have tolerated higher doses and that decreased survival in male rats may have compromised the sensitivity of the study for detecting neoplastic effects. Dr. Bishop replied that survival in high dose male rats was greater than 70% at 18 months and greater than 50% up until the last 2 weeks of the study.

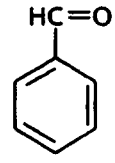
Dr. Garman moved that the Technical Report on benzaldehyde be accepted with the addition of a statement in the Conclusions that female rats and male and female mice could have tolerated higher doses, with the inclusion of statistical values for pancreatic hyperplasia in male rats, and with the conclusions as written for male and female rats, no evidence of carcinogenic activity, and for male and female mice, some evidence of carcinogenic activity.

Dr. Ashby seconded the motion. Dr. Mirer offered an amendment that the level of evidence in male rats be changed to equivocal evidence of carcinogenic activity, based on increased incidences of adenomas and hyperplasia of the pancreas and of mononuclear cell leukemia. Dr. McKnight seconded the amendment, which was defeated by a vote of six to two (Drs. McKnight and Mirer). The original motion by Dr. Garman was then accepted by seven affirmative votes and one negative vote (Dr. Klaassen).

I. INTRODUCTION

Physical and Chemical Properties
Environmental Occurrence
Use and Production
Human Exposure
Human Toxicity
Metabolism
Genetic Toxicity
Animal Toxicity
Carcinogenic/Anticarcinogenic Activity
Study Rationale

I. INTRODUCTION



BENZALDEHYDE

CAS No. 100-52-7

C_7H_6O Molecular weight 106.1

Synonyms: Artificial almond oil; artificial essential oil of almond; benzenecarbonal; benzene carbaldehyde; benzoic aldehyde; phenylmethanal

Physical and Chemical Properties

Benzaldehyde is a colorless liquid at room temperature; it boils at 179° C, solidifies at −56.5° C, and may become yellowish upon storage (Merck, 1983). Benzaldehyde has an odor like volatile almond oil and a burning aromatic taste. Although benzaldehyde is relatively insoluble in water (1:350), it is miscible with alcohol, ether, and oils. It oxidizes to benzoic acid in air.

Environmental Occurrence

Benzaldehyde is a natural constituent of several species of plants (especially almond kernels) and insects. It is present as cyanogenic glucoside (amygdalin) in the kernels of bitter almond, peach, apricot, and other Prunus species and in various parts of other plants. Free benzaldehyde has been reported in several essential oils, notably hyacinth, citronella, orris, cinnamon, sassafras, labdanum, and patchouli (Fenaroli, 1975). It has been identified in the defensive excretions of harvester ants and millipedes and as a major constituent in male pheromones of several noctuid Lepidoptera and in alarm pheromones of Trigonoma stingless bees (Opdyke, 1976). Low concentrations of benzaldehyde have been detected in exhaust from internal combustion engines and in wastewater effluent from industrial and municipal sources (Commission of the European Communities, 1976; Shackelford and Keith, 1976; Verschueren, 1977).

Use and Production

The use and production of benzaldehyde were reviewed by Williams (1978). Benzaldehyde can be produced synthetically by chlorination of toluene to benzal chloride, which is then hydrolyzed by reaction with lime (Vogel, 1959; Bedoukian, 1967), but the primary method of synthesis is by oxidation of toluene, where it is produced as a coproduct with benzoic acid. The estimated U.S. production of benzaldehyde in 1981 was approximately 75,000 tons (approximately 68×10^6 kg), up from 1975 estimates of just over 4,000 tons (approximately 3.6×10^6 kg). Benzaldehyde was in public use before the 1900's and is on the list of food additives "generally-recognized-as-safe" (GRAS), which are approved by the U.S. Food and Drug Administration for use in food. It has a variety of uses in the food and beverage, pharmaceutical, perfume, soap, and dyestuff industries, but it is used primarily as an intermediate in the synthesis of flavoring and fragrance agents, including aromatic alcohols. Its use in fragrances alone is estimated by the Research Institute for Fragrance Materials, Inc., to be approximately 75,000 pounds (34,000 kg) per year (Opdyke, 1976). Concentrations of benzaldehyde reportedly range from 36 to 840 ppm when used directly as a flavoring agent in various food and beverage products, such as alcoholic and nonalcoholic beverages, ice cream, candy, gelatins, puddings, and chewing gum (Fenaroli, 1975). It also has some use as a solvent for oils, resins, some cellulose ethers, cellulose acetate, and nitrate and is a useful pharmaceutical vehicle for administering bromides and other salts, especially when a low salt content is desired (Osol, 1980).

Human Exposure

Humans are exposed to benzaldehyde daily through foodstuffs; Zlatkis and Liebich (1971)

reported that it was among 300 volatile constituents detected in the urine of 10 adults. Based on a 1970-71 survey conducted by the Flavoring Extract Manufacturers' Association and the National Academy of Sciences/National Research Council (FEMA and NAS/NRC, 1978), Kluwe et al. (1983) estimated that 48.2 mg benzaldehyde per day is ingested by adults from food stuffs. The Acceptable Daily Intake (ADI) level for benzaldehyde, listed by the Council of Europe (1974) as 4 mg/kg, was given as an unconditional 0-5 mg/kg in a monograph published by the Joint Expert Committee on Food Additives (FAO/WHO, 1967). No standards for exposure limits in the workplace have been developed, but the Workplace Environmental Exposure Level Guide, published by the American Industrial Hygiene Association, recommends an 8-hour time-weighted-average (TWA) limit of 8.7 mg/m^3 and a 15-minute TWA limit of 17.4 mg/m^3 (AIHA, 1985).

Human Toxicity

Thomas (1958) reported that benzaldehyde, like other aldehydes and aldehyde-containing essential oils, was strongly irritating to the skin and may cause contact dermatitis in some humans. When tested by a maximization test at a concentration of 4% in petrolatum, benzaldehyde produced no sensitization reactions in any of 25 volunteers (Kligman, 1966); however, in patch tests using 5% benzaldehyde in Vaseline®, positive reactions were observed in 10/100 patients. Positive reactions occurred in patients with sensitivity to benzoic acid or vanillin (Hjorth, 1961).

In short-term studies on the inhibition of peptic activity, an effective dose (200-400 mg) of benzaldehyde was not toxic to humans (Kleeberg, 1959). However, benzaldehyde is described as being narcotic to humans at high concentrations. From two case studies, one in which a woman committed suicide by consuming an oral dose of 50-60 ml and a second in which a man was revived from near death after consuming an oral dose of 40 ml of *o*-hydroxybenzaldehyde (salicylaldehyde) (Dadlez, 1928), it is estimated that an oral dose of 600-900 mg/kg benzaldehyde would probably be lethal to humans in the absence of prompt treatment.

Metabolism

Benzaldehyde is extensively metabolized in mammals. There are two potential metabolic reactions involving the carbonyl group of benzaldehyde. One involves reaction of the carbonyl carbon with nucleophilic groups of certain amino acids or nucleic acid bases (either in the free state or as components of protein or DNA macromolecules) through formation of a Schiff base. The primary products of these reactions would be covalently bound adducts to macromolecules. Although formation of such covalently bonded adducts to proteins have been reported with acetaldehyde (Dellarco, 1988), no reports of the formation of such adducts by benzaldehyde were found in the literature. However, reported effects of benzaldehyde on various membrane functions, such as glucose and nucleoside uptake, were postulated to be the result of its interactions with plasma membrane proteins through formation of a Schiff base with amino groups in the cell membrane (Dornish et al., 1988).

The primary reaction in the metabolism of benzaldehyde is enzymatic oxidation or reduction of the carbonyl group to produce benzoyl or benzyl derivatives such as benzoic acid and benzyl alcohol, which may subsequently be conjugated for rapid excretion. In early studies, Friedmann and Turk (1913) and Bray et al. (1951) identified rapid oxidation to benzoic acid, with subsequent glycine conjugation and excretion as hippuric acid, as the major metabolic pathway in dogs and rabbits. No significant excretion of benzoyl glucuronide was observed. In 1988, Laham et al. reported that more than 80% of benzaldehyde given to New Zealand white rabbits in a single oral dose of 350 or 750 mg/kg was excreted in the urine as products of oxidative or reductive metabolism; they confirmed that the predominant urinary metabolite (65%-70%) was the glycine conjugate hippuric acid. However, they also identified other urinary metabolites, including the glucuronide conjugate benzoyl glucuronic acid (8.8% and 11.2%); free benzoic acid (1.6% and 1.4%); the glucuronide conjugate of benzyl alcohol, benzyl glucuronide (2.9% and 3.0%); and trace amounts of benzylmercapturic acid (*N*-acetyl-*S*-benzyl-L-cysteine). After intraperitoneal injection to female albino rats, 29.3% (21%-37%) of the injected benzaldehyde was reportedly

excreted in the urine as hippuric acid; this was only about 10% less than the 47% rate of conversion of benzoic acid to hippuric acid (Teuchy et al., 1971). Honecker (1975) also reported that benzaldehyde, as a cleavage product of amphetaminil, was rapidly converted to hippuric acid in the blood, brain, and adipose tissue of rats and then excreted in the urine. Laham and Potvin (1987) also demonstrated that benzaldehyde administered by gavage at 400, 750, or 1,000 mg/kg to Sprague Dawley rats was partly converted to benzylmercapturic acid and excreted in the urine; they suggested that benzylmercapturic acid was formed through glutathione conjugation in the presence of specific glutathione *S*-transferases. Laham et al. (1988), however, found no benzyl alcohol or benzyl sulfate ester present in rabbits. In in vitro experiments, Robertson and Dunstan (1972) demonstrated that benzaldehyde could be reduced to benzyl alcohol by the action of an aromatic aldehyde-ketone reductase from rabbit kidney, but not by alcohol dehydrogenase and hydroxysteroid dehydrogenase from rabbit liver, thus showing organ specificity for the reduction process.

Genetic Toxicity

Although it possesses a structurally alerting, electrophilic, carbonyl carbon (Ashby and Tennant, 1988), benzaldehyde is generally nongenotoxic. Benzaldehyde was not mutagenic in Salmonella gene mutation assays (Florin et al., 1980; Kasamaki et al., 1982; Haworth et al., 1983; Nohmi et al., 1985) or in the Drosophila sex-linked recessive lethal assay (Woodruff et al., 1985). It exhibited genotoxic activity in the mouse lymphoma assay (McGregor et al., 1990) and in assays for sister chromatid exchanges in both Chinese hamster ovary (CHO) cells (Galloway et al., 1987) and human lymphocytes (Jansson et al., 1988). Induction of chromosomal aberrations by benzaldehyde was also reported in Chinese hamster lung cells at a dose stated to be 50 nM (5.3 ng/ml) (Kasamaki et al., 1982); however, the National Toxicology Program (NTP), using concentrations of benzaldehyde which were approximately 10,000 times higher, found no increase in aberrations in CHO cells (Galloway et al., 1987). This basic pattern of no mutagenic activity in bacterial systems but possible weak clastogenic effects in some mammalian cell assays is also reflected in test results from metabolites of benzaldehyde, i.e., benzoic acid (Simmon and Kauhanen, 1978; Ishidate et al., 1984), hippuric acid (Milvy and Garro, 1976), and benzyl alcohol (Florin et al., 1980; Mortelmans et al., 1986; NTP, 1989a).

Animal Toxicity

Benzaldehyde caused moderate irritation when applied directly to the skin or eyes of rabbits exposed to 500 mg per day (Moreno, 1973). In rabbits, the dermal LD_{50} value for benzaldehyde was greater than 1,250 mg/kg (Moreno, 1973); by subcutaneous injection, the LD_{50} value was reported to be 5,000 mg/kg (Fassett, 1963). In rats, a 5,000 mg/kg dose of benzaldehyde was reported to be lethal when given by subcutaneous injection but was not always lethal when given by intraperitoneal injection (Macht, 1922). Oral LD_{50} values for benzaldehyde were reported to be 1,000 mg/ kg in guinea pigs and 1,300 mg/kg in rats (Jenner et al., 1964). The LD_{50} value for mice administered benzaldehyde by intraperitoneal injection was reported to be 1,020 mg/kg; no deaths occurred at 848 mg/kg, and 100% of the mice receiving 1,113 mg/kg died (Caujolle, 1956). In one study, benzaldehyde fed to male rats at 1,000 ppm for 27-28 weeks and to female rats at 10,000 ppm for 16 weeks reportedly produced "no effect" on growth or hematology at the end of the study and no macroscopic or microscopic changes in the liver, kidney, spleen, heart, testis, abdominal and thoracic vicera, hind leg, forebone, bone marrow, or muscle (Hagan et al., 1967).

Carcinogenic/Anticarcinogenic Activity

No carcinogenicity studies of benzaldehyde in animals were found in the literature. Schweinsberg et al. (1986) suggested that benzaldehyde, as an identified metabolite of *N*-nitroso-*N*-methylbenzylamine (NMBA), might be responsible for induction of squamous cell papillomas of the lung observed with NMBA. Benzyl alcohol, one of the purported metabolites of benzaldehyde and certainly a chemical that is metabolized to benzaldehyde, did not induce any neoplasms when administered in 2-year studies by gavage at 200 or 400 mg/kg to F344/N rats and at 100 or 200 mg/kg to $B6C3F_1$ mice (NTP, 1989a).

Benzaldehyde had been proposed as a possible chemotherapeutic agent (Buick et al., 1979), based initially on reports of antitumor activity with extracts of figs in which benzaldehyde was considered to be the active component (Takeuchi et al., 1978). Benzaldehyde per se was reported to have antitumor activity in several experimental systems (Zundel et al., 1978) as well as a high degree of clinical activity when administered as tablets or suppositories of β-cyclodextrin benzaldehyde to cancer patients who had undergone unsuccessful chemotherapy or radiation therapy (Kochi et al., 1980). It has also been shown to inhibit the growth of transformed mouse and simian cells (Nambata et al., 1982) and to inhibit cell cycling (Pettersen et al., 1983). However, Taetle and Howell (1983) reported that benzaldehyde lacked significant activity against most human neoplasms tested in vitro, and MacEwen (1986) was able to elicit only minimal antitumor activity in vivo in dogs and cats given oral doses of 10 mg/kg benzaldehyde. Benzaldehyde has been shown to affect various membrane functions, including glucose and nucleoside uptake, by interacting with plasma membrane proteins (possibly through formation of a Schiff base with amino groups of the cell membrane) (Dornish et al., 1988) and to inhibit protein synthesis; it is speculated that these activities contribute to the limited antitumor activity observed.

Study Rationale

Benzaldehyde was nominated for carcinogenicity studies primarily because of its high production volume and substantial human exposure, and incidentally because of structural considerations as the parent compound of the aromatic aldehyde group and a general paucity of data on these compounds. Gavage was chosen as the route of administration that would most accurately monitor exposure amounts and mimic the oral exposure of humans.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZALDEHYDE

PREPARATION AND CHARACTERIZATION OF DOSE FORMULATIONS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZALDEHYDE

Benzaldehyde (USP-grade) was obtained as a clear, colorless liquid in two lots from the Aldrich Chemical Company (lot no. JE5718HE) and from the R.W. Greeff Company (lot no. 005-0120). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). Both lots of the study chemical were identified as benzaldehyde by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

The purity of both lots studied was determined by elemental analysis, Karl Fischer water analysis, gas chromatography, reaction of the carbonyl group with hydroxylammonium chloride in the presence of 2-dimethylaminoethanol and back-titration with perchloric acid of the excess hydroxylamine, and titration with sodium hydroxide to determine free acid content (as benzoic acid). Gas chromatography by two different systems detected no impurities having areas of 0.1% or greater relative to the area of the major peak for either lot. Comparison of the results of the two titration methods indicated the presence of approximately 0.38% benzoic acid in lot no. JE5718HE and approximately 0.29% benzoic acid in lot no. 005-0120.

Based on the results of all analyses, the purity of lot no. JE5718HE was determined to be greater than 99% and that of lot no. 005-0120 to be approximately 99%.

The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy. The stability of the bulk chemical during the toxicology studies was monitored by gas chromatography and titration of the free acid. No deterioration of benzaldehyde was observed during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE FORMULATIONS

The stability of benzaldehyde dissolved in corn oil at approximately 80 mg/ml was determined at the analytical laboratory. The chemical was found to be stable at room temperature in the dark for 14 days when stored in sealed vials. A small (approximately 5%) loss occurred when benzaldehyde in corn oil was exposed to air and light for 3 hours at room temperature under simulated dosing conditions. Dose formulations were prepared once per week and were stored in the dark at room temperature under nitrogen for a maximum of 14 days throughout the studies.

Periodic ultraviolet analysis of the dose formulations was conducted at the study laboratory and at the analytical chemistry laboratory. During the 13-week studies, all dose formulations were found to be within specifications (Table G3).

During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals. For the benzaldehyde studies, it was estimated that the formulations were prepared within $\pm 10\%$ of the target concentrations approximately 96% (77/80) of the time throughout the studies (Table G4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G5).

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 18 days before the studies began. The rats were 7 weeks old when placed on study, and the mice were 8 weeks old.

Groups of five rats of each sex were administered 0, 100, 200, 400, 800, or 1,600 mg/kg benzaldehyde in corn oil by gavage, 5 days a week for 12 doses over 16 days. Groups of five mice of each sex were administered 0, 200, 400, 800, 1,600, or 3,200 mg/kg on the same schedule.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed twice per day and were weighed on days 1 and 8 and at the end of the studies. Details of animal maintenance are presented in Table 1. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZALDEHYDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
Rats--0, 100, 200, 400, 800, or 1,600 mg/kg benzaldehyde in corn oil by gavage; mice--0, 200, 400, 800, 1,600, or 3,200 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 50, 100, 200, 400, or 800 mg/kg benzaldehyde in corn oil by gavage; mice--0, 75, 150, 300, 600, or 1,200 mg/kg; dose vol--5 ml/kg	Rats and male mice--0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage; female mice--0, 300, or 600 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
1/26/81	4/1/81	Rats--1/18/82; mice--male: 1/19/82; female: 3/2/82
Date of Last Dose		
2/10/81	6/30/81	Rats--1/6/84; mice--male: 1/16/84; female: 2/20/84
Duration of Dosing		
12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 (rats and female mice) or 104 (male mice) wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 16-d studies	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and 1 × mo thereafter
Necropsy and Histologic Examinations		
Necropsy performed on all animals	Necropsy performed on all animals; the following tissues were examined histologically for all vehicle control and high dose animals, all rats receiving 400 mg/kg, and all male mice receiving 600 mg/kg: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pharynx, pituitary gland, preputial or clitoral gland (rats), prostate/testes or ovaries/uterus, salivary glands, small intestine, spinal cord (high dose male rats), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder; spleen, stomach, and kidneys examined for female mice receiving 600 mg/kg; and kidneys and liver examined for male mice receiving 300 mg/kg	Necropsy performed on all animals; the following tissues examined histologically for all vehicle control and high dose animals, low dose male rats, and all animals dying before the end of the studies: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, eyes (rats), femur including marrow, gallbladder (mice), gross lesions and tissue masses, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), rectum, salivary glands, sciatic nerve, skin, spinal cord (rats), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined for low dose groups include adrenal glands, bone, brain, clitoral gland, eyes, gross lesions, heart, kidneys, liver, lungs, pituitary gland, spinal cord, spleen, and stomach for female rats and gross lesions and stomach for mice
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source		
Charles River Breeding Laboratories (Kingston, NY)	Harlan Industries (Indianapolis, IN)	Frederick Cancer Research Facility (Frederick, MD)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZALDEHYDE (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory		
Southern Research Institute	Southern Research Institute	Southern Research Institute
Method of Animal Identification		
Ear punch	Ear mark	Ear mark and toe clip
Time Held Before Study		
18 d	14 d	Rats--20 d; mice--19 d
Age When Placed on Study		
Rats--7 wk; mice--8 wk	Rats--6 wk; mice--8 wk	Rats--8 wk; mice--male: 8 wk; female: 9 wk
Age When Killed		
Rats--9-10 wk; mice--10-11 wk	Rats--19-21 wk; mice--21-23 wk	113 wk
Necropsy or Kill Dates		
Rats--2/11/81-2/14/81; mice--2/11/81-2/13/81	7/1/81-7/14/81	Rats--1/16/84-1/20/84; mice--male: 1/24/84-1/26/84; female: 2/28/84-3/1/84
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to cages according to one table of random numbers and to groups according to a table of random numbers	Same as 16-d studies	Same as 16-d studies
Diet		
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding		
Beta Chips (Northeastern Products, Inc., Warrensburg, NY)	Same as 16-d studies	Same as 16-d studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages		
Polycarbonate (Lab Products, Inc., Garfield, NJ)	Same as 16-d studies	Same as 16-d studies
Cage Filters		
Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--73°-76° F; hum--37%-59%; fluorescent light 12 h/d; 15 room air changes/h	Temp--72°-80° F; hum--39%-59%; fluorescent light 12 h/d; 15 room air changes/h	Temp--62°-89° F; hum--25%-86%; fluorescent light 12 h/d; 15 room air changes/h

administration of benzaldehyde and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 5- to 6-week old male and female $B6C3F_1$ mice were obtained from Harlan Industries, observed for 14 days, assigned to weight classes, and randomly distributed to cages. Prior to dosing, cages were randomly distributed to the various dose groups. Independent tables of random numbers were used for all distributions. Rats were 6 weeks old when placed on study, and mice were 8 weeks old. Further experimental details are summarized in Table 1.

Groups of 10 rats of each sex were administered 0, 50, 100, 200, 400, or 800 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 75, 150, 300, 600, or 1,200 mg/kg on the same schedule.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded on day 0, once per week, and at the end of the studies.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Complete histopathologic examinations were performed on vehicle controls, 400 and 800 mg/kg rats, 600 mg/kg male mice, and 1,200 mg/kg mice. Tissues and groups examined are listed in Table 1. Results of the 16-day and 13-week studies have been published by Kluwe et al. (1983).

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex and groups of 50 male mice were administered 0, 200, or 400 mg/kg benzaldehyde in corn oil by gavage, 5 days per week for 103 (rats) or 104 (male mice) weeks. Groups of 50 female mice were administered 0, 300, or 600 mg/kg, 5 days per week for 103 weeks. Because of a large number of gavage-associated deaths, the study with female mice was restarted.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Facility. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. Rats were placed on study at 8 weeks of age, male mice at 8 weeks of age, and female mice at 9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the National Toxicology Program (NTP) Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. After July 1982, cages were rotated vertically, top to bottom, within dose groups and on the racks. Racks were rotated counterclockwise. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead. Some tissues were excessively autolyzed or missing, and thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (see Table 1) were performed on all high dose and vehicle control animals and on low dose animals dying before the end of the study. Since mortality in the high dose group of male rats exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the low dose group. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues (male rats: pancreas, thyroid gland, kidney, spleen, and liver; female rats: eye, pituitary gland, spleen, and liver; male and female mice: forestomach), and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends.

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

Statistical Methods

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

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such

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

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

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

Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

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

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

SIXTEEN-DAY STUDIES

All rats that received 1,600 mg/kg died on day 2; 2/5 males and 2/5 females that received 800 mg/kg also died before the end of the studies (Table 2). Compound-related clinical signs were not seen in animals that survived to the end of the studies. Final mean body weights of rats that received 800 mg/kg were 14% lower than those of the vehicle con-trols for males and 11% lower for females. The final mean body weights of rats in other dosed groups were similar to those of vehicle controls. No compound-related gross lesions were observed.

THIRTEEN-WEEK STUDIES

Six of 10 males and 3/10 females that received 800 mg/kg and 1/10 females that received 400 mg/kg died before the end of the studies (Table 3). One vehicle control female rat also died. The final mean body weight of male rats that received 800 mg/kg was 26% lower than that of vehicle controls. Final mean body weights of dosed and vehicle control female rats were similar.

Compound-related lesions were seen at 800 mg/kg but not at 400 mg/kg. In the brain, these lesions included degeneration and necrosis of the

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF BENZALDEHYDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	168 ± 5	238 ± 6	+70 ± 2	
100	5/5	156 ± 4	228 ± 6	+72 ± 3	96
200	5/5	160 ± 4	229 ± 4	+69 ± 4	96
400	5/5	169 ± 4	240 ± 4	+71 ± 3	101
800	(d) 3/5	168 ± 5	204 ± 8	+31 ± 3	86
1,600	(e) 0/5	171 ± 2	(f)	(f)	(f)
FEMALE					
0	5/5	120 ± 4	151 ± 2	+31 ± 2	
100	5/5	112 ± 2	140 ± 2	+28 ± 1	93
200	5/5	114 ± 2	145 ± 3	+31 ± 1	96
400	5/5	120 ± 4	154 ± 4	+34 ± 2	102
800	(g) 3/5	112 ± 3	135 ± 2	+21 ± 5	89
1,600	(e) 0/5	120 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 6,6
(e) Day of death: all 2
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 6,12

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZALDEHYDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	110 ± 1	340 ± 5	+230 ± 5	
50	10/10	108 ± 2	338 ± 6	+230 ± 6	99
100	10/10	108 ± 2	346 ± 6	+238 ± 6	102
200	10/10	111 ± 2	349 ± 6	+238 ± 5	103
400	10/10	109 ± 2	329 ± 8	+220 ± 8	97
800	(d) 4/10	107 ± 2	252 ± 5	+147 ± 5	74
FEMALE					
0	(e) 9/10	95 ± 2	203 ± 3	+107 ± 4	
50	10/10	92 ± 2	196 ± 4	+104 ± 3	97
100	10/10	92 ± 2	203 ± 3	+111 ± 2	100
200	10/10	91 ± 2	200 ± 4	+109 ± 3	99
400	(f) 9/10	93 ± 2	203 ± 3	+111 ± 2	100
800	(g) 7/10	93 ± 2	213 ± 4	+118 ± 4	105

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of survivors ± standard error of the mean
(d) Week of death: 5,9,9,11,12,13
(e) Week of death: 1
(f) Week of death: 9
(g) Week of death: 10,12,13

cerebellum and necrosis of the neurons in the hippocampus. Hyperplasia and/or hyperkeratosis of the forestomach, characterized by a mild-to-moderate thickening of the squamous epithelium, occurred in both males and females in the 800 mg/kg groups. Degeneration of the liver, necrosis of the liver (males only), and degeneration or necrosis of the tubular epithelium in the kidney also occurred at the highest dose (Table 4).

The cellular degeneration and necrosis present in the granular and Purkinje cell layers of the cerebellum were focal to multifocal in distribution and minimal to marked in severity; in males, mineralization was also present in the areas of necrosis. Areas of involvement had pyknotic and karyorrhectic nuclei with dark eosinophilic cytoplasm. As the lesion progressed, these foci contained nuclear debris and cellular detritus. Often, these nuclear fragments were undergoing early mineralization evidenced by formation of oval or round basophilic mineralized concretions of various sizes. As the mineralization increased in severity, it could be identified at low power magnification as corpa amylacea surrounded by halos. The lesion in the granular layer often extended into the Purkinje cell layer, entrapping neurons and resulting in cell death. Occasional Purkinje cells could be seen deep within the granular layer. The hippocampal lesions consisted of disruptions of the pyramidal and molecular layers, with loss of normal architecture observable at low magnification. At higher magnification, the molecular layer had focal areas of necrosis with foci of pale, eosinophilic "ghost cells." The pyramidal layers had focal areas of cellular necrosis consisting of pyknotic, basophilic nuclei that were undergoing karyorrhexis. In milder cases, nuclear debris in this zone was often the only lesion observed.

TABLE 4. NUMBERS OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZALDEHYDE

Site/Lesion	Dose (mg/kg)					
	Male			Female		
	0	400	800	0	400	800
Number examined	10	10	10	9	10	10
Brain/cerebellum						
Degeneration	0	0	**9	0	0	**10
Necrosis	0	0	**10	0	0	**10
Mineralization	0	0	**7	0	0	0
Brain/hippocampus						
Necrosis	0	0	**(a)6	0	0	**10
Forestomach						
Hyperplasia	0	0	**6	0	0	**8
Hyperkeratosis	0	0	*5	0	0	**6
Liver						
Degeneration	0	0	*4	0	0	*4
Necrosis	0	0	3	0	0	0
Kidney/tubule						
Degeneration	0	0	*4	0	0	*4
Necrosis	0	0	3	0	0	3

(a) Six brains were examined.
*P<0.05 vs. vehicle controls by Fisher exact test
**P<0.01 vs. vehicle controls by Fisher exact test

Dose Selection Rationale: Because of the various lesions observed at 800 mg/kg but not at 400 mg/kg, doses selected for rats for the 2-year studies were 200 and 400 mg/kg benzaldehyde, administered in corn oil by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control rats were similar throughout the studies (Table 5 and Figure 1).

TABLE 5. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control Number Weighed	200 mg/kg Av. Wt. (grams)	200 mg/kg Wt. (percent of vehicle controls)	200 mg/kg Number Weighed	400 mg/kg Av. Wt. (grams)	400 mg/kg Wt. (percent of vehicle controls)	400 mg/kg Number Weighed
MALE								
1	160	50	161	101	50	161	101	50
2	210	50	209	100	50	208	99	50
3	235	50	233	99	50	235	100	50
4	253	50	255	101	50	257	102	50
5	272	50	273	100	50	275	101	50
6	288	50	290	101	50	291	101	50
7	304	50	303	100	50	305	100	50
8	317	50	317	100	50	319	101	50
9	328	50	325	99	50	329	100	50
10	337	50	334	99	50	339	101	50
11	348	50	345	99	50	348	100	50
12	356	50	353	99	50	356	100	50
13	361	50	362	100	50	364	101	50
17	383	50	383	100	50	387	101	50
22	409	50	408	100	50	415	101	50
26	424	50	424	100	50	429	101	49
30	433	50	434	100	50	442	102	49
35	447	50	449	100	50	459	103	48
39	459	50	459	100	49	466	102	48
43	468	50	472	101	49	477	102	47
49	478	50	482	101	49	491	103	46
54	487	50	493	101	49	501	103	46
58	488	50	499	102	49	503	103	42
62	491	50	504	103	49	506	103	42
66	492	50	505	103	49	511	104	40
70	493	49	508	103	49	510	103	40
74	496	48	511	103	48	520	105	38
78	490	47	506	103	48	512	104	37
82	488	47	506	104	47	520	107	34
86	481	45	499	104	46	514	107	32
90	481	41	498	104	45	510	106	30
94	474	41	483	102	44	507	107	29
98	467	41	478	102	41	499	107	29
102	464	40	471	102	37	497	107	26
Mean for weeks								
1-13	289.9		289.2	100		291.3	100	
17-49	437.6		438.6	100		445.8	102	
54-102	484.0		497.0	103		508.5	105	
FEMALE								
1	128	50	128	100	50	128	100	50
2	148	50	150	101	50	151	102	50
3	159	50	159	100	50	160	101	50
4	168	50	168	100	50	169	101	50
5	176	50	176	100	50	179	102	50
6	181	50	181	100	50	183	101	50
7	186	50	185	99	50	189	102	50
8	190	50	188	99	50	195	103	50
9	193	50	193	100	50	199	103	50
10	195	50	197	101	50	201	103	50
11	197	50	199	101	50	204	104	50
12	201	50	202	100	50	207	103	50
13	203	50	204	100	50	209	103	50
17	211	50	213	101	50	217	103	50
22	221	50	222	100	50	229	104	49
26	227	50	230	101	50	235	104	47
30	231	50	234	101	50	241	104	47
35	239	50	244	102	50	248	104	46
39	249	50	252	101	50	254	102	45
43	257	50	260	101	50	264	103	44
49	273	50	273	100	50	279	102	44
54	286	49	288	101	50	296	104	44
58	296	49	300	101	50	305	103	44
62	301	49	305	101	50	308	102	44
66	310	49	313	101	50	315	102	44
70	316	48	321	102	50	322	102	44
74	319	48	325	102	48	327	103	(a) 42
78	321	46	323	101	48	327	102	41
82	321	46	330	103	47	329	102	39
86	322	44	330	102	46	331	103	38
90	325	43	334	103	45	334	103	37
94	320	42	334	104	43	335	105	36
98	326	40	336	103	40	334	102	34
102	331	36	341	103	34	336	102	30
Mean for weeks								
1-13	178.7		179.2	100		182.6	102	
17-49	238.5		241.0	101		245.9	103	
54-102	314.9		321.5	102		323.0	103	

(a) The number of animals weighed was lower than the number of animals surviving.

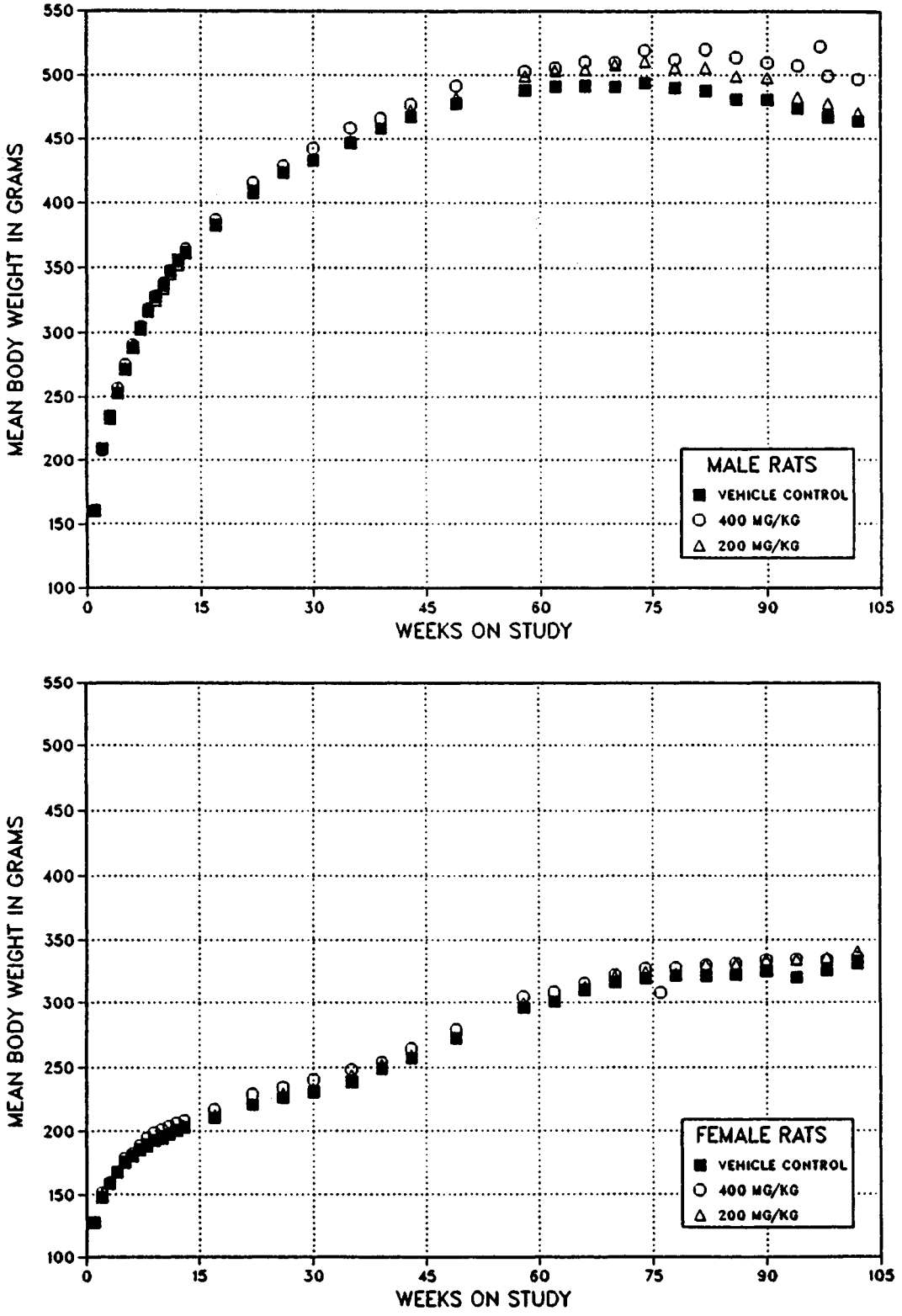


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED BENZALDEHYDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered benzaldehyde at the doses used in these studies and for vehicle controls are shown in Table 6 and in the Kaplan and Meier curves in Figure 2. The survival of the high dose group of male rats was significantly lower than that of the vehicle controls after day 373; no other significant differences were observed between any groups of either sex.

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

	Vehicle Control	200 mg/kg	400 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	3	9	12
Moribund kills	10	12	17
Animals surviving until study termination	37	29	21
Mean survival (days)	698	694	608
Survival P values (b)	<0.001	0.176	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	4	1	9
Moribund kills	13	16	12
Animals surviving until study termination	33	33	29
Mean survival (days)	692	699	632
Survival P values (b)	0.302	1.000	0.352

(a) First day of termination period: male--729; female--730
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

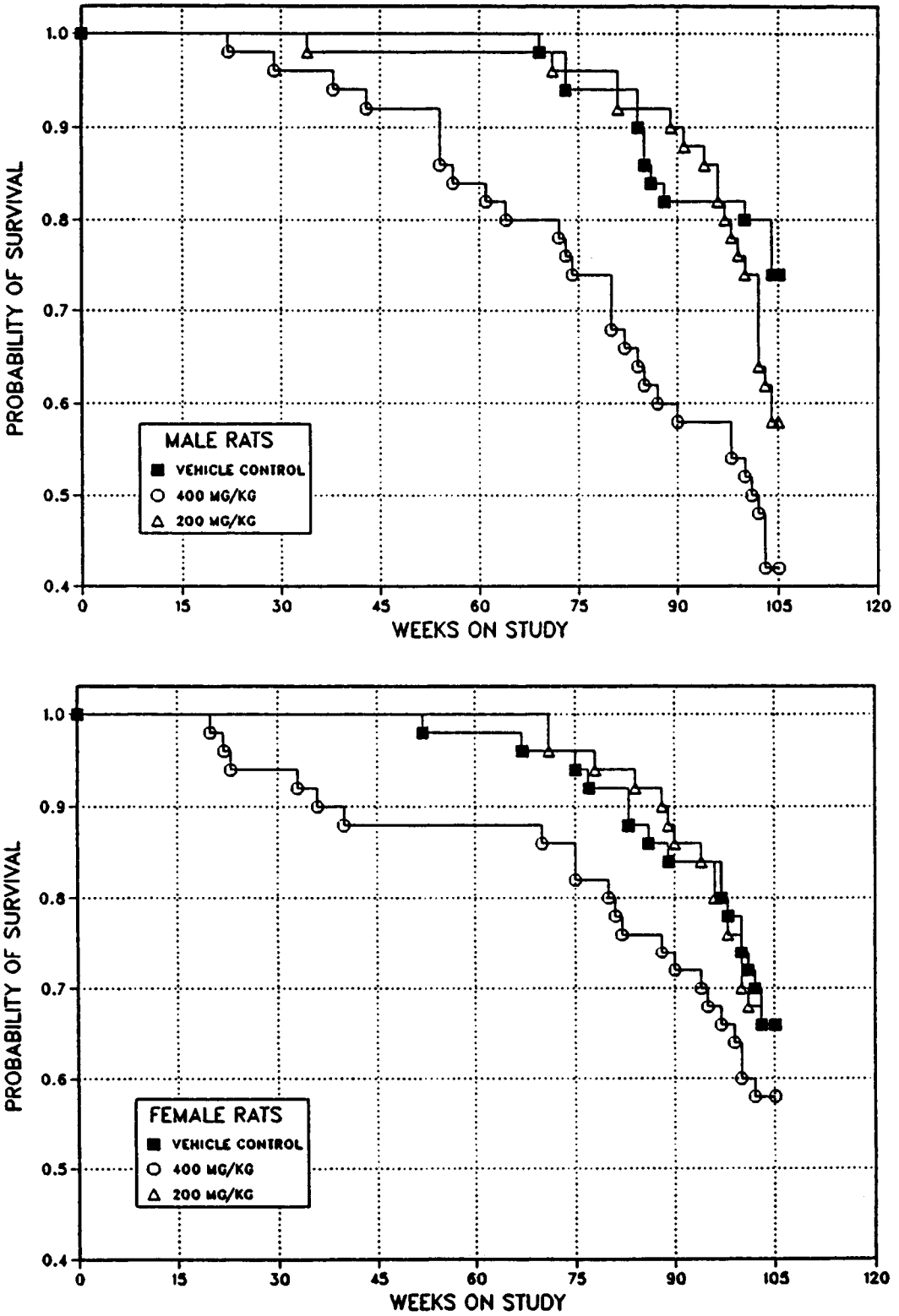


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED BENZALDEHYDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the pancreas, mesothelium, hematopoietic system, and forestomach.

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

Pancreas: Hyperplasia and adenomas of the exocrine pancreas were marginally increased in high dose male rats; the incidence of adenomas in the high dose group was significantly greater than that in the vehicle controls (Table 7). The incidence of adenomas in the high dose group, however, was well within the range of historical corn oil vehicle control incidences of pancreatic acinar cell neoplasms at the study laboratory (0/49-11/50, 22%) and only slightly greater than the mean historical control incidence at the study laboratory (36/397, 9%).

Hyperplasia and adenomas are part of a morphologic continuum varying from small lesions, 1 mm or less in diameter, to nodular masses up to 10 mm in diameter. Smaller lesions have minimal alteration in growth pattern and minimal cellular atypia, whereas larger ones exhibit progressively greater alterations and atypia. Because there is no exclusive criterion that distinguishes adenomas from hyperplasia, size (in addition to growth pattern and cellular characteristics) is used to categorize these proliferative lesions. Generally, lesions smaller than 3 mm in diameter with slight accentuation of the tubular pattern were diagnosed as hyperplasia, whereas those larger than 3 mm were diagnosed as adenomas.

TABLE 7. PANCREATIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Hyperplasia			
Overall Rates	6/49 (12%)	6/49 (12%)	12/48 (25%)
Terminal Rates	5/36 (14%)	6/29 (21%)	9/21 (43%)
Day of First Observation	724	729	373
Logistic Regression Tests	P=0.015	P=0.484	P=0.025
Adenoma (b)			
Overall Rates	3/49 (6%)	2/49 (4%)	7/48 (15%)
Terminal Rates	3/36 (8%)	1/29 (3%)	6/21 (29%)
Day of First Observation	729	711	697
Logistic Regression Tests	P=0.024	P=0.532N	P=0.038

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of acinar cell adenomas or carcinomas (combined) at study laboratory (mean ± SD): 36/397 (9% ± 9%); historical incidence in NTP studies: 107/2,011 (5% ± 7%)

Mesothelium: Malignant mesotheliomas of the tunica vaginalis and/or peritoneum (mesentery) were marginally increased in dosed male rats (Table 8). The incidence of 5/50 in the low dose group slightly exceeded the highest incidence observed in a corn oil vehicle control group (4/50, 8%) at the study laboratory. Because there was no significant increase in the high dose group and because the incidence in the low dose group was only marginally increased relative to the mean historical corn oil vehicle control incidence at the study laboratory (15/450, 3%), the malignant mesotheliomas were considered to be unrelated to the administration of benzaldehyde.

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a significant positive trend; the incidences in the dosed groups were significantly greater than that in the vehicle controls (Table 9). The increase in leukemia in dosed male rats is largely due to an increase in early stage-1 leukemia. The following criteria were used in staging the extent and severity of the leukemia:

Stage 1. Spleen not enlarged or only slightly enlarged, with small numbers of mononuclear cells in the red pulp; no or very few mononuclear cells in the liver sinusoids and none in other organs.

Stage 2. Spleen moderately enlarged with moderate-to-large numbers of mononuclear cells in the red pulp; the architectural features, including lymphoid follicles and periarteriolar lymphocytic sheaths, remain intact. Minimal-to-moderate numbers of mononuclear cells are present in the sinusoids of the liver. Mononuclear cells may be evident in blood vessels in other organs, but aggregates/masses of neoplastic cells generally limited to spleen and liver.

Stage 3. Advanced disease with multiple organ involvement. Spleen usually markedly enlarged with effacement of normal architectural features by accumulated neoplastic cells. Liver moderately to markedly enlarged and nodular; hepatic parenchyma shows variable degenerative changes associated with the accumulation of neoplastic cells. Accumulation of neoplastic mononuclear cells in other organs such as the lung, lymph nodes, kidney, brain, adrenal gland or others.

Because of the relatively large proportion of stage-1 leukemia, the logistic regression test is believed to be more appropriate than the life table test for statistical analysis. No significant effect was seen on the incidences of stage-2 or stage-3 leukemia (combined). The slight increases in mononuclear cell leukemia observed in the dosed groups were not considered to be chemically related.

Forestomach: Squamous papillomas were seen in two high dose female rats; the historical incidence of forestomach neoplasms in corn oil vehicle control female F344/N rats is 9/2,085 (0.4%), and the highest observed incidence is 2/49. Hyperplasia of the mucosa was seen in 5/50 vehicle control, 2/50 low dose, and 3/50 high dose female rats.

TABLE 8. MESOTHELIAL TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Mesothelioma (b)			
Overall Rates	0/50 (0%)	5/50 (10%)	2/50 (4%)
Terminal Rates	0/37 (0%)	4/29 (14%)	1/21 (5%)
Day of First Observation		676	558
Logistic Regression Tests	P=0.167	P=0.031	P=0.233

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean ± SD): 15/450 (3% ± 3%); historical incidence in NTP studies: 78/2,099 (4% ± 3%)

TABLE 9. HEMATOPOIETIC SYSTEM TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Mononuclear Cell Leukemia (b)			
Overall Rates	10/50 (20%)	17/50 (34%)	16/50 (32%)
Terminal Rates	7/37 (19%)	13/29 (45%)	10/21 (48%)
Day of First Observation	508	632	373
Stage 1 (c)	4	10	7
Stage 2	1	3	2
Stage 3	5	4	7
All Stages			
Life Table Tests	P=0.003	P=0.026	P=0.006
Logistic Regression Tests	P=0.023	P=0.081	P=0.041
Stages 2 or 3 (combined)			
Overall Rates	6/50 (12%)	7/50 (14%)	9/50 (18%)
Terminal Rates	4/37 (11%)	4/29 (14%)	4/21 (19%)
Life Table Tests	P=0.050	P=0.361	P=0.072
Logistic Regression Tests	P=0.202	P=0.497	P=0.266

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of leukemia at study laboratory (mean ± SD): 45/450 (10% ± 8%); historical incidence in NTP studies: 361/2,099 (17% ± 9%)
(c) Number of rats with indicated stage of leukemia

III. RESULTS: MICE

SIXTEEN-DAY STUDIES

All mice that received 1,600 or 3,200 mg/kg died by day 3 (Table 10). One male that received 800 mg/kg died on day 10. Final mean body weights of dosed and vehicle control mice were similar. No compound-related gross lesions were observed.

THIRTEEN-WEEK STUDIES

Nine of 10 males and 1/10 females that received 1,200 mg/kg died during the first week (Table 11). The final mean body weight of males that received 600 mg/kg was 9% lower than that of vehicle controls. Final mean body weights of dosed and vehicle control female mice were similar. The only other compound-related effect in mice was a mild-to-moderate renal tubule degeneration that occurred in all 10 males that received 1,200 mg/kg and in 1 male that received 600 mg/kg.

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF BENZALDEHYDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.8 ± 0.4	27.0 ± 0.4	+2.2 ± 0.2	
200	5/5	24.0 ± 0.5	25.8 ± 0.7	+1.8 ± 0.2	96
400	5/5	24.8 ± 0.2	26.2 ± 0.6	+1.4 ± 0.4	97
800	(d) 4/5	25.8 ± 0.7	27.3 ± 0.9	+2.0 ± 0.4	101
1,600	(e) 0/5	25.0 ± 0.5	(f)	(f)	(f)
3,200	(e) 0/5	25.8 ± 0.2	(f)	(f)	(f)
FEMALE					
0	5/5	19.2 ± 0.4	21.6 ± 0.4	+2.4 ± 0.2	
200	5/5	18.6 ± 0.2	20.8 ± 0.2	+2.2 ± 0.2	96
400	5/5	19.0 ± 0.3	21.4 ± 0.2	+2.4 ± 0.2	99
800	5/5	19.2 ± 0.4	22.2 ± 0.5	+3.0 ± 0.4	103
1,600	(g) 0/5	18.8 ± 0.4	(f)	(f)	(f)
3,200	(e) 0/5	19.2 ± 0.2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 10
(e) Day of death: all 2
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 2,2,3,3,3

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZALDEHYDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.0 ± 0.3	35.0 ± 0.6	+10.0 ± 0.6	
75	10/10	24.3 ± 0.4	34.3 ± 0.8	+10.0 ± 0.6	98
150	10/10	24.2 ± 0.2	33.9 ± 0.7	+9.7 ± 0.7	97
300	10/10	24.3 ± 0.3	33.8 ± 0.7	+9.5 ± 0.5	97
600	10/10	24.1 ± 0.4	31.8 ± 0.9	+7.7 ± 0.6	91
1,200	(d) 0/10	24.1 ± 0.3	(e)	(e)	(e)
FEMALE					
0	10/10	19.5 ± 0.3	26.2 ± 0.6	+6.7 ± 0.4	
75	10/10	19.4 ± 0.2	26.0 ± 0.4	+6.6 ± 0.5	99
150	10/10	19.3 ± 0.3	27.5 ± 0.9	+8.2 ± 0.7	105
300	10/10	19.3 ± 0.2	25.9 ± 0.2	+6.6 ± 0.2	99
600	10/10	19.2 ± 0.4	25.5 ± 0.5	+6.3 ± 0.5	97
1,200	(f) 9/10	19.2 ± 0.4	27.0 ± 0.7	+7.9 ± 0.4	103

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: all 1 except one death during week 4
(e) No data are reported due to 100% mortality in this group.
(f) Week of death: 1

Dose Selection Rationale: Doses of benzaldehyde selected for male mice for the 2-year studies were 200 and 400 mg/kg, based on renal lesions in one male mouse given 600 mg/kg and in all of the male mice given 1,200 mg/kg for 13 weeks. Doses selected for female mice for the 2-year studies were 300 and 600 mg/kg because of the steep dose-response curve for mortality demonstrated in the 16-day and 13-week studies (survival--16-day study: 1,600 mg/kg, 0/5; 13-week study: 1,200 mg/kg, 9/10).

TWO-YEAR STUDIES

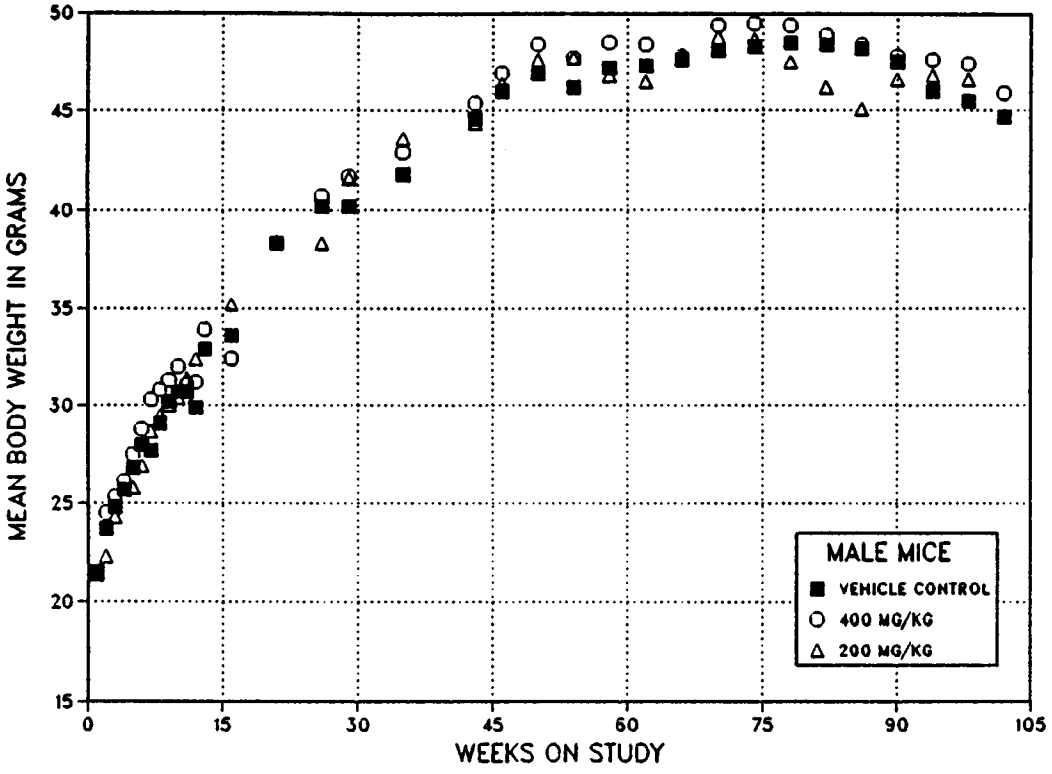
Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control mice were similar throughout the studies (Table 12 and Figure 3). No compound-related clinical signs were observed.

TABLE 12. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control Number Weighed	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of vehicle controls)	Low Dose Number Weighed	High Dose Av. Wt. (grams)	High Dose Wt. (percent of vehicle controls)	High Dose Number Weighed
MALE				**200 mg/kg**			**400 mg/kg**	
1	21.5	50	21.4	99.5	50	21.4	99.5	50
2	23.7	48	22.3	94.1	48	24.6	103.8	(a) 49
3	24.8	46	24.3	98.0	48	25.3	102.0	49
4	25.7	46	25.7	100.0	48	26.1	101.6	(a) 48
5	26.8	46	25.8	96.3	48	27.5	102.6	(a) 48
6	28.0	46	26.9	96.1	48	28.7	102.5	(a) 48
7	27.7	46	28.7	103.6	48	30.3	109.4	49
8	29.1	46	29.5	101.4	48	30.7	105.5	49
9	30.2	46	30.0	99.3	48	31.2	103.3	(a) 48
10	30.7	46	30.4	99.0	48	31.9	103.9	(a) 48
11	30.7	46	31.4	102.3	48	31.0	101.0	(a) 48
12	29.9	46	32.4	108.4	48	31.1	104.0	(a) 48
13	32.9	46	32.9	100.0	48	33.8	102.7	(a) 48
16	33.6	46	35.2	104.8	48	32.3	96.1	(a) 48
21	38.3	46	38.4	100.3	48	38.1	99.5	(a) 48
26	40.2	46	38.3	95.3	48	40.6	101.0	(a) 48
29	40.2	46	41.6	103.5	48	41.6	103.5	(a) 48
35	41.8	46	43.6	104.3	47	42.7	102.2	49
39	43.9	46	44.4	101.1	47	45.4	103.4	49
43	44.6	46	44.4	99.6	47	45.3	101.6	(a) 47
46	46.1	46	46.4	100.7	46	46.7	101.3	(a) 47
50	46.9	46	47.6	101.5	46	48.3	103.0	(a) 47
54	46.2	46	47.7	103.2	46	47.6	103.0	(a) 46
58	47.2	46	46.8	99.2	46	48.4	102.5	(a) 46
62	47.3	46	46.5	98.3	46	48.4	102.3	(a) 46
66	47.6	44	47.9	100.6	46	47.8	100.4	(a) 46
70	48.1	44	48.8	101.5	46	49.4	102.7	45
74	48.3	44	48.7	100.8	44	49.5	102.5	45
78	48.5	44	47.5	97.9	43	49.4	101.9	43
82	48.4	43	46.2	95.5	42	48.9	101.0	43
86	48.2	41	45.1	93.6	39	48.4	100.4	38
90	47.5	40	46.6	98.1	39	47.8	100.6	38
94	46.0	39	46.8	101.7	38	47.6	103.5	37
98	45.5	36	46.6	102.4	38	47.4	104.2	35
102	44.7	35	44.8	100.2	35	45.9	102.7	33
Mean for weeks								
1-13	27.8		27.8	100		28.7	103	
16-50	41.7		42.2	101		42.3	101	
54-102	47.2		46.9	99		48.2	102	
FEMALE				**300 mg/kg**			**600 mg/kg**	
1	17.4	50	17.4	100.0	50	17.4	100.0	50
2	18.7	50	18.4	98.4	50	18.8	100.5	50
3	19.5	49	18.9	96.9	50	19.7	101.0	50
4	20.8	49	19.6	94.2	50	19.5	93.7	50
5	21.6	49	21.2	98.1	50	21.3	98.6	50
6	22.3	49	22.0	98.7	50	22.1	99.1	50
7	22.5	49	22.6	100.4	50	22.3	99.1	50
8	23.3	49	22.9	98.3	50	23.0	98.7	50
9	23.4	49	23.5	100.4	50	23.5	100.4	50
10	23.6	49	23.3	98.7	50	24.0	101.7	50
11	24.3	49	23.6	97.1	50	23.6	97.1	50
12	25.0	49	24.3	97.2	50	24.5	98.0	50
13	24.8	49	24.7	99.6	50	25.3	102.0	50
15	25.6	49	25.2	98.4	50	25.6	100.0	50
20	26.5	49	25.5	96.2	49	25.2	95.1	50
23	27.9	49	27.8	99.6	49	27.7	99.3	50
29	28.2	49	29.4	104.3	49	29.4	104.3	50
33	30.1	49	30.4	101.0	49	30.5	101.3	50
37	30.8	49	31.4	101.9	49	31.7	102.9	50
40	32.0	49	31.5	98.4	49	32.5	101.6	50
44	34.2	49	33.8	98.8	49	33.5	98.0	50
48	34.7	49	35.7	102.9	49	35.1	101.2	50
52	35.9	49	34.0	94.7	49	36.3	101.1	49
56	36.2	49	36.3	100.3	49	36.8	101.7	49
58	37.5	49	37.4	99.7	49	37.4	99.7	49
62	39.1	49	38.9	99.5	48	39.3	100.5	49
66	38.7	48	39.0	100.8	46	39.5	102.1	47
70	38.4	47	41.2	107.3	45	40.3	104.9	47
74	40.3	45	41.5	103.0	44	40.9	101.5	45
78	40.7	42	41.7	102.5	43	42.1	103.4	43
82	40.8	41	41.3	101.2	41	40.8	100.0	43
86	40.3	40	42.1	104.5	40	41.2	102.2	43
90	40.7	39	42.3	103.9	38	41.4	101.7	40
94	41.1	35	42.8	104.1	35	42.1	102.4	40
98	42.0	33	42.0	100.0	31	42.0	100.0	40
102	39.6	31	42.0	106.1	30	42.2	106.6	37
Mean for weeks								
1-13	22.1		21.7	98		21.9	99	
15-52	30.6		30.5	100		30.8	101	
56-102	39.6		40.7	103		40.5	102	

(a) The number of animals weighed was lower than the number of animals surviving.



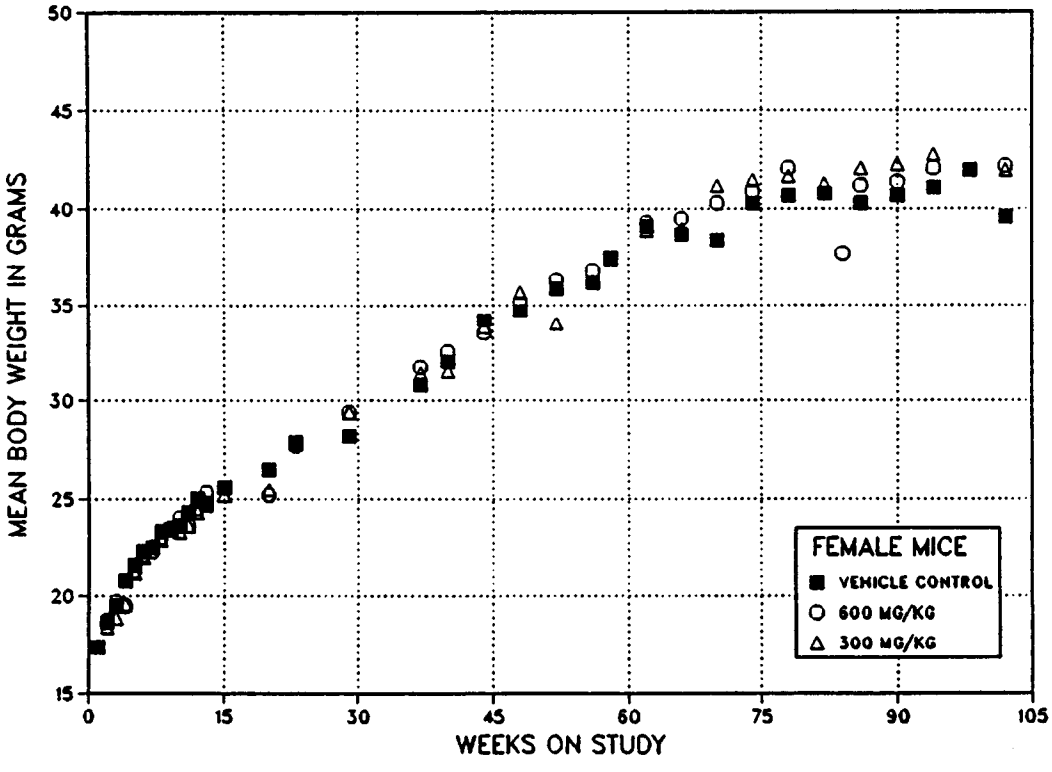


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED BENZALDEHYDE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice administered benzaldehyde at the doses used in these studies and for vehicle controls are shown in Table 13 and in the Kaplan and Meier curves in Figure 4. No significant differences were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

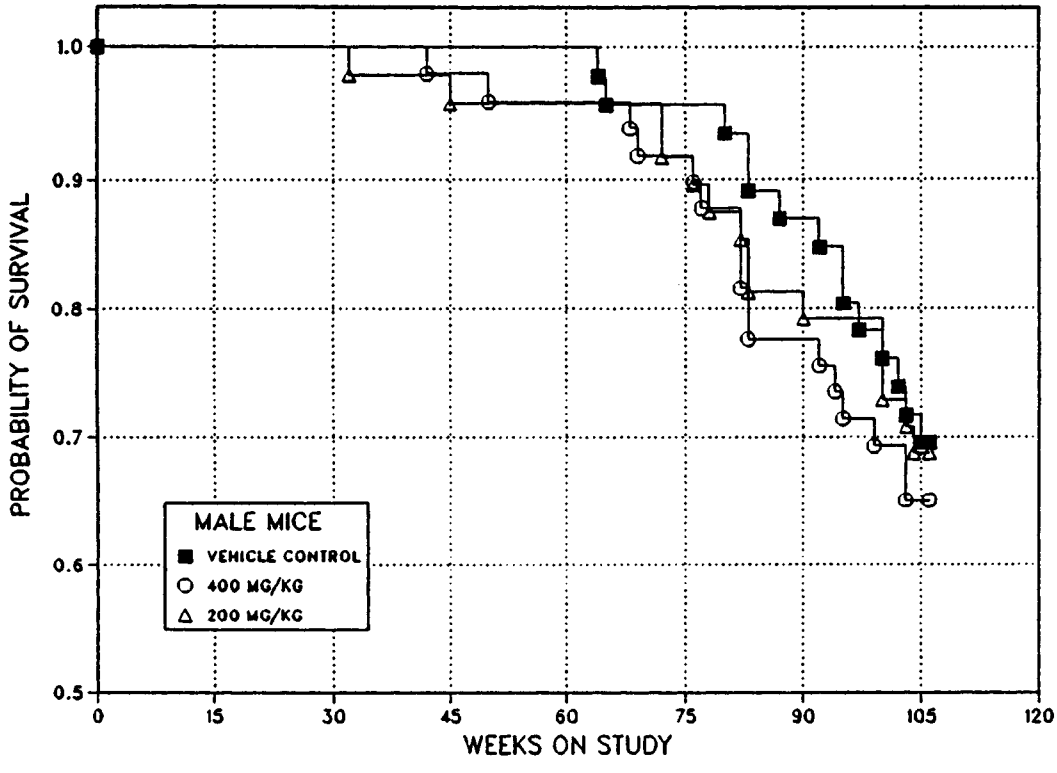
This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach.

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

TABLE 13. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

	Vehicle Control	Low Dose	High Dose
MALE (a)		**200 mg/kg**	**400 mg/kg**
Animals initially in study	50	50	50
Natural deaths	5	4	4
Moribund kills	9	11	13
Killed accidentally	4	2	2
Animals surviving until study termination	32	33	31
Mean survival (days)	646	656	662
Survival P values (b)	0.592	0.989	0.654
FEMALE (a)		**300 mg/kg**	**600 mg/kg**
Animals initially in study	50	50	50
Natural deaths	7	8	8
Moribund kills	11	13	7
Killed accidentally	2	2	0
Animals surviving until study termination	30	27	(c) 35
Mean survival (days)	662	658	683
Survival P values (b)	0.521	0.695	0.589

(a) First day of termination period: male--736; female--729
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(c) One of the animals died a natural death during the termination period and was combined, for statistical purposes, with those killed at termination.



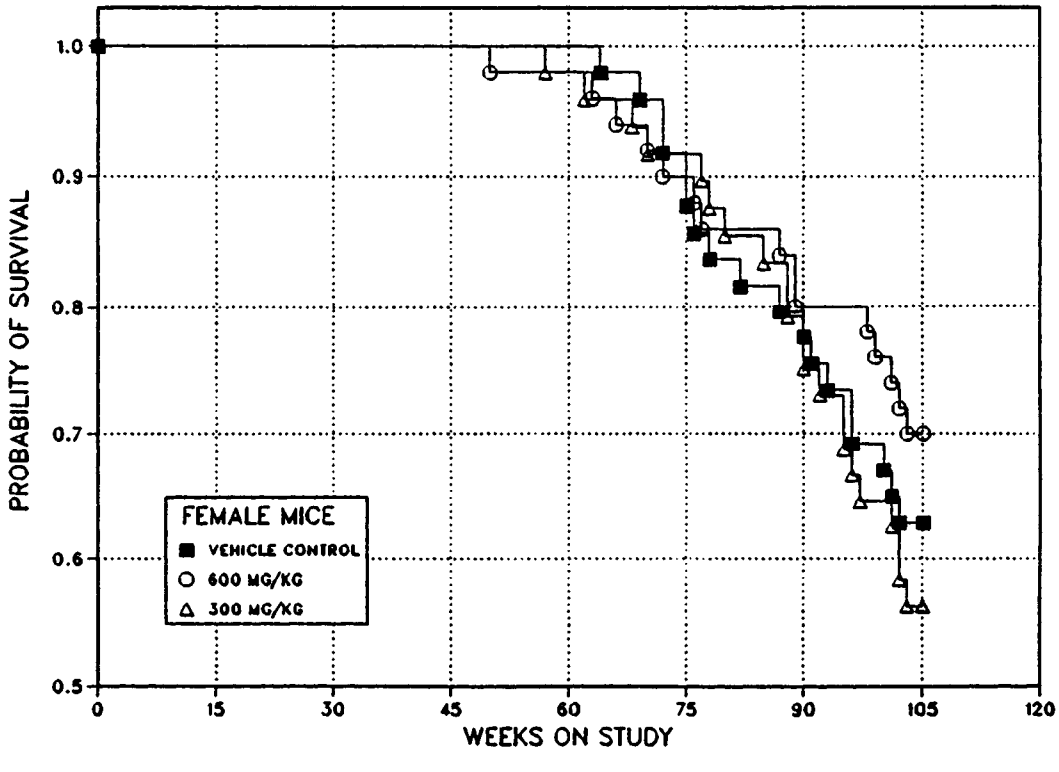


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED BENZALDEHYDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Focal hyperplasia and squamous cell papillomas were increased in dosed male and female mice; the incidences of squamous cell papillomas in low and high dose female mice were significantly greater than that in vehicle controls (Table 14).

Focal hyperplasia of the forestomach was characterized by a localized region of increased thickness of the stratified squamous epithelium. In the less severe lesions the surface of the epithelium was irregular or slightly folded, whereas in the more advanced lesions the epithelium was more extensively folded, producing short papillary projections with a narrow core of connective tissue (Figures 5 and 6). The squamous cell papillomas exhibited greater complexity of the papillae and the formation of a stalk (Figure 7).

A squamous cell carcinoma was diagnosed in a single high dose female mouse by the pathologist at the study laboratory. The original histologic section of this lesion was examined by the Pathology Working Group, which did not confirm a diagnosis of neoplasia; they recommended that additional sections of the lesion be examined. Additional sections were prepared and examined by the laboratory and National Toxicology Program (NTP) staff pathologists. Although the laboratory pathologist preferred the diagnosis of squamous cell carcinoma, the NTP pathologists believed the lesion represented an inflamed epithelial cyst with hyperplasia of the overlying epithelium (Figure 8). Thus, this lesion was not included in Table 14 and was not considered when benzaldehyde-related effects were interpreted.

TABLE 14. FORESTOMACH LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE (a)

	Vehicle Control	Low Dose	High Dose
MALE		**200 mg/kg**	**400 mg/kg**
Hyperplasia			
Overall Rates	7/50 (14%)	8/50 (16%)	**16/50 (32%)
Squamous Papilloma (b)			
Overall Rates	1/50 (2%)	2/50 (4%)	5/50 (10%)
Terminal Rates	1/32 (3%)	1/33 (3%)	5/31 (16%)
Day of First Observation	736	541	736
Logistic Regression Tests	P=0.057	P=0.502	P=0.094
FEMALE		**300 mg/kg**	**600 mg/kg**
Hyperplasia			
Overall Rates	12/50 (24%)	*23/50 (46%)	**39/50 (78%)
Squamous Papilloma (c)			
Overall Rates	0/50 (0%)	5/50 (10%)	6/50 (12%)
Terminal Rates	0/30 (0%)	3/27 (11%)	5/35 (14%)
Day of First Observation		591	526
Logistic Regression Tests	P=0.020	P=0.032	P=0.020

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of squamous cell papillomas or carcinomas (combined) at study laboratory (mean ± SD): 8/445 (2% ± 4%); historical incidence in NTP studies: 39/2,033 (2% ± 3%)
(c) Historical incidence of squamous cell papillomas or carcinomas (combined) at study laboratory (mean ± SD): 8/446 (2% ± 3%); historical incidence in NTP studies: 33/2,047 (2% ± 3%)
*P<0.05 vs. the vehicle controls
**P<0.01 vs. the vehicle controls

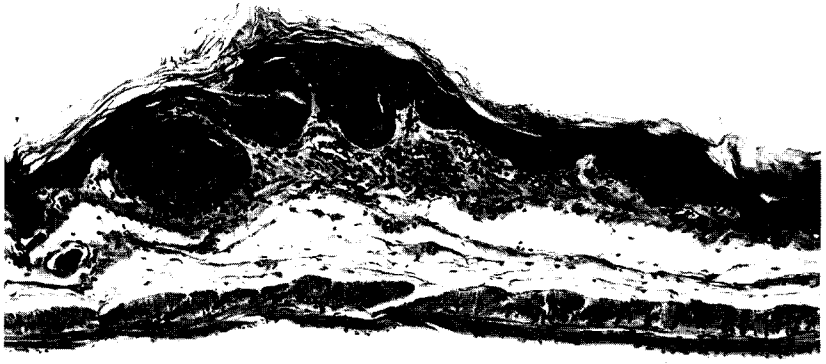


Figure 5. Minimal focal hyperplasia of the stratified squamous epithelium of the forestomach in high dose female mouse CID no. 791. Original magnification, 25×.

Figure 6. Mild focal hyperplasia of the stratified squamous epithelium of the forestomach in high dose female mouse CID no. 814. Note the folded, thickened epithelium. Original magnification, 25×.

Figure 7. Squamous cell papilloma of the forestomach in high dose female mouse CID no. 803. The stalk connecting the papilloma to the forestomach is not in the plane of section. Original magnification, 5×.

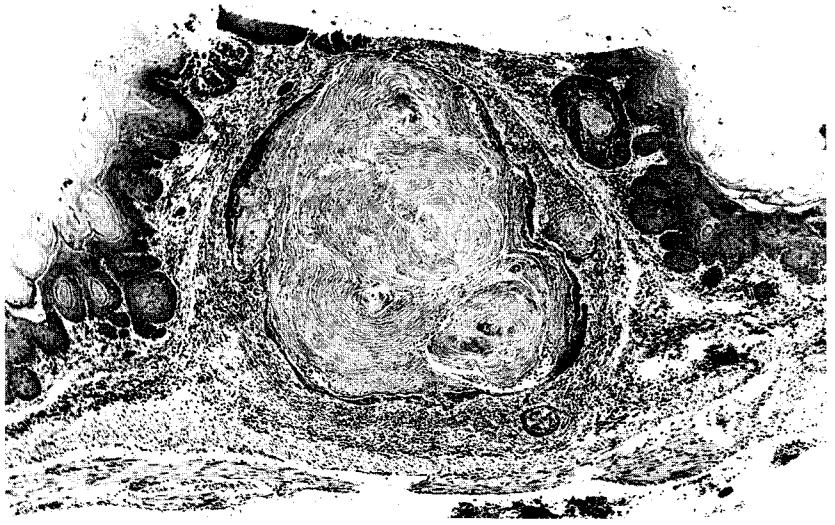


Figure 8. Lesion in forestomach of high dose female mouse CID no. 853 diagnosed as squamous cell carcinoma by the laboratory pathologist. Note the large keratin-filled cavity lined by squamous epithelium and surrounded by inflammatory cells. The adjacent epithelium is hyperplastic. Original magnification, 10×.

Benzaldehyde was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested according to a preincubation protocol with doses up to 1,000 µg/plate (slight toxicity noted at this dose) in both the presence and absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table H1). Results of *S. typhimurium* mutagenicity tests performed in a second laboratory with benzaldehyde doses of up to 3,333 µg/plate in strains TA100, TA102, and TA104 with and without induced rat or mouse liver S9 were also negative (Table H1). Benzaldehyde gave a positive response in the absence of exogenous metabolic activation for induction of trifluorothymidine resistance in mouse L5178Y/TK cells at the highest dose tested in each of two trials; no tests were performed with activation (McGregor et al., 1990; Table H2). In cytogenetic tests with Chinese hamster ovary (CHO) cells, benzaldehyde induced sister chromatid exchanges at doses of 50 and 160 µg/ml in the absence of S9 and at a dose of 1,600 µg/ml in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Galloway et al., 1987; Table H3). No induction of chromosomal aberrations was observed in CHO cells treated with up to 500 µg/ml benzaldehyde in the absence of S9 or with up to 1,600 µg/ml with S9 (Galloway et al., 1987; Table H4). No significant induction of sex-linked recessive lethal mutations was observed in the germ cells of male *Drosophila melanogaster* administered benzaldehyde at a concentration of 1,150 ppm by feeding or 2,500 ppm by injection (Woodruff et al., 1985; Table H5). The experimental procedures and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Benzaldehyde is an aromatic aldehyde used in the food, beverage, perfume, pharmaceutical, soap, and dyestuff industries. It was nominated for carcinogenicity studies on the basis of its high production volume (75,000 tons in 1981) and substantial human exposure (an estimated average of 48.2 mg is ingested daily by adult humans [Kluwe et al., 1983]) and also on structural considerations as the parent compound of the aromatic aldehyde group.

Sixteen day, 13-week, and 2-year studies of benzaldehyde were conducted in F344/N rats and B6C3F$_1$ mice. Benzaldehyde was administered by gavage in corn oil for most accurate control of exposure amounts and to mimic oral human exposure. The chemical is known to be oxidized rapidly to benzoic acid when exposed to air, and thus, administration in diet mixtures was not considered appropriate. The benzaldehyde used in these studies was at least 99% pure; less than 0.5% benzoic acid was present.

The major chemically related lesions observed in the 13-week studies in male and female rats were focal degeneration and necrosis of neurons in the granular cell layer of the cerebellum, necrosis of neurons in the hippocampus, degeneration and necrosis of hepatocytes and of the epithelial cells in the proximal convoluted tubules of the kidney, and hyperplasia and hyperkeratosis of the stratified squamous epithelium of the forestomach (Kluwe et al., 1983). These lesions were observed only in animals given 800 mg/kg. In the 2-year studies of benzaldehyde, no clearly chemically related lesions were observed at these sites in rats given 400 mg/kg for up to 2 years. However, uncommonly occurring squamous cell papillomas were observed in the forestomach of two high dose female rats; the highest incidence of forestomach papillomas observed in a single group of historical corn oil vehicle control female F344/N rats at the study laboratory is 1/50 (mean, 0.7%) and at any National Toxicology Program (NTP) laboratory is 2/49 (mean, 0.4%). Because squamous cell papillomas of the forestomach were seen in only two female rats in the high dose group and because there was a lack of supporting hyperplasia, these papillomas were not considered to be due to the administration of benzaldehyde.

There were significant increases in the incidences of pancreatic acinar cell hyperplasia and/or adenomas in male rats at the high dose; the dose-related trend was also significant. However, unpublished results from NTP studies demonstrate that pancreatic acinal cell adenomas found in rats gavaged with corn oil do not transplant and, therefore, are not autonomous neoplasms. Based on the nontransplantability of the tumors, the variable and high incidence of these tumors observed in the vehicle controls at the study laboratory, and the marginal increase in the incidence of adenomas only at the high dose (an incidence that was within the historical range), the observed incidences of pancreatic acinar cell tumors and hyperplasia were not considered as evidence of carcinogenic activity for benzaldehyde.

Chemically related lesions in the kidney of male mice given 1,200 mg/kg benzaldehyde for 13 weeks were similar to those observed in male and female rats. Lesions in the brain, forestomach, or liver were not seen in male or female mice, and lesions in the kidney were not seen in female mice. In the 2-year studies in mice, lesions considered to be related to benzaldehyde were observed only in the forestomach, where there were dose-related increased incidences of focal hyperplasia in males and females and a dose-related increased incidence of uncommonly occurring squamous cell papillomas in females. The incidences of squamous cell papillomas in low dose (5/50) and high dose (6/50) female mice were significant, compared with none in vehicle controls; the incidence in the high dose group slightly exceeded the highest incidence of forestomach neoplasms observed in corn oil vehicle control female B6C3F$_1$ mice in NTP studies (5/44, 11%), and the incidences in both dosed groups were substantially above the background incidence in NTP studies (1.6%). Although the incidence of forestomach papillomas in the high dose group of male mice (5/50) was not significantly greater than that in the vehicle control group (1/50), it exceeded the highest historical incidence of forestomach squamous cell neoplasms either in studies at this laboratory (4/49, 8%) or in any other NTP study in which male B6C3F$_1$ mice were administered corn oil by gavage (4/46, 9%) and was substantially above the

mean historical incidence (1.9%). The increases in papillomas in the forestomach of both male and female mice, as well as the concomitant increase in hyperplasia, are considered to be due to administration of benzaldehyde. The etiology of squamous cell papillomas in the forestomach and their progression are not specifically known. The role of chronic irritation in this process is uncertain. There was no clear histologic evidence of progression from hyperplasia to malignancy in these studies.

Although little is known concerning the potential for forestomach papillomas to regress or progress to malignant neoplasms, the forestomach epithelium is a stratified squamous epithelium like that of the skin, and squamous cell papillomas of the forestomach are morphologically similar to those of the skin (Odashima, 1979). In the two-stage model of skin carcinogenesis in which one application of an initiator is followed by repeated applications of a promoter, a preponderance of papillomas is induced and 90%-95% of these have been shown to regress (Burns et al., 1976a,b; Colburn, 1980). The skin tumor promoter 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) has been considered capable of "enhancing" skin carcinogenesis initiated by other chemicals and was thought to need continuous application or the tumors would regress. Studies of the induction and regression kinetics of papillomas suggest that there may be two populations of papillomas: a large population that regresses after cessation of chemical application (conditional or promoter-dependent papillomas) and a much smaller population of autonomous papillomas that persist (Burns et al., 1976a,b). At present, it is unknown whether autonomous papillomas arise directly from conditional papillomas in a sequential series of events beginning with a single cell or whether they arise from different populations of cells (Chu et al., 1987).

In initiation-promotion studies (reviewed by Hennings et al., 1983), more than 90% of the squamous cell carcinomas develop from papillomas, but the conversion rate is reported to be low. Other studies on the population kinetics of papillomas of the skin indicate that promoters generally do not increase the conversion rate of papillomas to carcinomas, whereas initiators do. Repeated applications of initiators induce primarily squamous cell carcinomas with few papillomas. These studies suggest that further genetic changes to cells within a papilloma are required for the development of malignant neoplasms.

Squamous cell papillomas of the forestomach are considered neoplasms, albeit benign. The increased incidences of these neoplasms induced by benzaldehyde might be considered as marked in female mice because of the significant increases at both dose levels and the significant dose-related trend. In male mice, the increase might be considered marked because the incidence in the high dose group was substantially greater than the mean historical incidence and exceeded the highest incidence at this laboratory or in any other NTP study. Although mice of each sex exhibited attendant increases in hyperplasia, there was a total absence of squamous cell carcinomas in both males and females. Of the seven other NTP chemicals that have been found to induce forestomach neoplasms in mice when administered by corn oil by gavage (Table 15), none has produced only squamous cell papillomas in both males and females. Thus, due to the lack of evidence for progression to malignancy, what may have appeared to be clear evidence of carcinogenic activity in mice exposed to benzaldehyde was considered as some evidence at best.

Of the eight NTP chemicals shown to induce forestomach neoplasms in B6C3F$_1$ mice when administered in corn oil by gavage, six are mutagenic in the majority of genotoxicity tests (Table 16; benzaldehyde and benzyl acetate are the exceptions) and all caused increases in the incidence of nonneoplastic (hyperplasia) and neoplastic (papillomas or carcinomas) lesions of the forestomach in mice of each sex. Of the chemicals listed, only two (benzyl acetate and dimethylvinyl chloride) induced neoplasms at other sites in mice; several induced neoplasms at other sites in rats.

TABLE 15. INCIDENCES OF FORESTOMACH SQUAMOUS CELL NEOPLASMS IN B6C3F$_1$ MICE GIVEN VARIOUS CHEMICALS IN CORN OIL BY GAVAGE FOR UP TO TWO YEARS

Study	Male			Female			Reference
	Dose (mg/kg)	Papilloma	Carcinoma	Dose (mg/kg)	Papilloma	Carcinoma	
1,2-Dibromo-3-chloropropane							
	0	0/20	0/20	0	0/20	0/20	NCI, 1978
	80-130	0/46	43/46	60-130	0/50	50/50	(TR 28)
	160-260	0/49	47/49	120-260	0/48	47/48	
Benzyl acetate							
	0	3/49	1/49	0	0/50	0/50	NTP, 1986a
	500	3/48	1/48	500	0/50	0/50	(TR 250)
	1,000	9/49	2/49	1,000	4/48	0/48	
Diglycidyl resorcinol ether							
	0	0/47	0/47	0	0/47	0/47	NTP, 1986b
	50	4/49	14/49	50	5/49	12/49	(TR 257)
	100	10/50	25/50	100	10/49	23/49	
Ethyl acrylate							
	0	0/48	0/48	0	1/50	0/50	NTP, 1986c
	100	4/47	2/47	100	4/49	1/49	(TR 259)
	200	9/50	5/50	200	5/48	2/48	
3-Chloro-2-methylpropene							
	0	3/49	0/49	0	0/50	0/50	NTP, 1986d
	100	19/49	5/49	100	15/48	1/48	(TR 300)
	200	30/49	7/49	200	29/44	2/44	
Dichlorvos							
	0	1/50	0/50	0	5/49	0/49	NTP, 1989b
	10	1/50	0/50	20	6/49	0/49	(TR 342)
	20	9/50	0/50	40	18/50	2/50	
Dimethylvinyl chloride							
	0	0/48	1/48	0	0/50	0/50	NTP, 1986e
	100	42/47	3/47	100	1/47	40/47	(TR 316)
	200	35/44	8/44	200	3/43	36/43	
Benzaldehyde							
	0	1/50	0/50	0	0/50	0/50	Current studies
	200	2/50	0/50	300	5/50	0/50	
	400	5/50	0/50	600	6/50	0/50	

TABLE 16. GENETIC TOXICITY OF VARIOUS CHEMICALS THAT INDUCE FORESTOMACH NEOPLASMS IN B6C3F$_1$ MICE AFTER ADMINISTRATION IN CORN OIL BY GAVAGE FOR UP TO TWO YEARS

Study	Salmonella	Mouse Lymphoma	In Vitro Cytogenetics		Drosophila	
			SCE	Aberration	Sex-linked Rec. Lethals	Reciprocal Translocation
1,2-Dibromo-3-chloropropane	+	+	+	+	+	+
Benzyl acetate	–	+	–	–	On test	On test
Diglycidyl resorcinol ether	+	+	+	+	+	+
Ethyl acrylate	–	+	+	+	–	–
3-Chloro-2-methylpropene	–	+	+	+	On test	On test
Dichlorvos	+	+	+	+		
Dimethylvinyl chloride	+	+	+	–	+	+
Benzaldehyde	–	+	+	–	–	

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

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzaldehyde for male or female F344/N rats receiving 200 or 400 mg/kg per day. There was *some evidence of carcinogenic activity* of benzaldehyde for male or female B6C3F$_1$ mice, as indicated by increased incidences of squamous cell papillomas and hyperplasia of the forestomach. Female rats and male and female mice might have been able to tolerate higher doses.

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

V. REFERENCES

V. REFERENCES

1. American Industrial Hygiene Association (AIHA) (1985) Workplace Environmental Exposure Level Guide. Cincinnati: AIHA.

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

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

4. Ashby, J.; Tennant, R.W. (1988) Chemical structure, Salmonella mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat. Res. 204:17-115.

5. Bedoukian, P.Z. (1967) Benzaldehyde. Perfumery and Flavoring Synthetics, 2nd ed. New York: Elsevier Publishing Co., pp. 48-54.

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

7. Bray, H.G.; Thorpe, W.V.; White, K. (1951) Kinetic studies of the metabolism of foreign organic compounds. 1. The formation of benzoic acid from benzamide, toluene, benzyl alcohol and benzaldehyde and its conjugation with glycine and glucuronic acid in the rabbit. Biochem. J. 48:88-96.

8. Buick, R.N.; Messner, H.A.; Till, J.E.; McCulloch, E.A. (1979) Cytotoxicity of adriamycin and daunorubicin for normal and leukemia progenitor cells of man. J. Natl. Cancer Inst. 62:249-255.

9. Burns, F.J.; Vanderlaan, M.; Sivak, A.; Albert, R.E. (1976a) Regression kinetics of mouse skin papillomas. Cancer Res. 36:1422-1427.

10. Burns, F.J.; Vanderlaan, M.; Snyder, E.; Albert, R.E. (1976b) Induction and progression kinetics of mouse skin papillomas. Slaga, T.J.; Sivak, A.; Boutwell, R.K., Eds.: Carcinogenesis, Vol. 2: Mechanisms of Tumor Promotion and Cocarcinogenesis. New York: Raven Press.

11. Caujolle, F.; Meynier, D.; Auriac, P.; Frajdenrach, S.; Troplent, L. (1956) Toxicity of phthalic aldehydes. C. R. Acad. Sci. 243:1933.

12. Chu, K.C.; Brown, C.C.; Tarone, R.E.; Tan, W.Y. (1987) Differentiating among proposed mechanisms for tumor promotion in mouse skin with the use of multievent model for cancer. J. Natl. Cancer Inst. 79:789-796.

13. Clive, D.; Johnson, K.O.; Spector, J.F.S.; Batson, A.G.; Brown, M.M.M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

14. Colburn, N.H. (1980) Tumor promotion and preneoplastic progression. Slaga, T.J., Ed.: Carcinogenesis, Vol. 5: Modifiers of Chemical Carcinogenesis. New York: Raven Press.

15. Commission of the European Communities (1976) A Comprehensive Listing of Polluting Substances Which Have Been Identified in Various Fresh Waters, Effluent Discharges, Aquatic Animals and Plants and Bottom Sediments, 2nd ed. Copenhagen: Commission of the European Communities, European Cooperation and Coordination in the Field of Scientific and Technical Research, p. 77.

16. Council of Europe (1974) Natural Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances, Partial Agreement in the Social and Public Health Field. List 1, No. 101. Strasbourg, p. 145.

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

18. Dadlez, J. (1928) Toxicity of benzoic acid and salicyl aldehydes in man. C. R. Soc. Biol. 99: 1038-1039.

19. Dellarco, V.L. (1988) A mutagenicity assessment of acetaldehyde. Mutat. Res. 195:1-20.

20. Dinse, G.E.; Haseman, J.K. (1986) Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. Fundam. Appl. Toxicol. 6:44-52.

21. Dinse, G.E.; Lagakos, S.W. (1983) Regression analysis of tumour prevalence data. J. R. Stat. Soc. C32:236-248.

22. Dornish, J.M.; Petterson, E.O.; Oftebro, R. (1988) Modulation of *cis*-dichlorodiamineplatinum (*cis*-DDP) induced cell inactivation by aldehydes: Protection by benzaldehyde (Benz); potentiation by cinnamaldehyde (Cinn). Proc. Annu. Meet. Am. Assoc. Cancer Res. 29:475 (Abstr.).

23. Fassett, D.W. (1963) Aldehydes and acetals. Patty, F.A., Ed.: Industrial Hygiene and Toxicology, Vol. 2, 2nd ed. New York: Interscience Publishers, p. 1987.

24. Fenaroli's Handbook of Flavor Ingredients (1975) 2nd ed., Vol. 2. Furia, T.E.; Bellanca, N., Eds. Cleveland: The Chemical Rubber Company Press.

25. Flavoring Extract Manufacturers' Association and National Academy of Sciences/National Research Council (FEMA and NAS/NRC) (1978).

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

27. Food and Agriculture Organization/World Health Organization (FAO/WHO) (1967) Toxicological evaluation of some flavouring substances and non-nutritive sweetening agents. Food and Agriculture Organization Nutr. Mtg. Rep. Ser. No. 44A. Geneva: World Health Organization, Food Add. 68.33, p. 10.

28. Friedmann, E.; Turk, W. (1913) Behavior of benzaldehyde in the animal body. Biochem. Z. 55:425.

29. Galloway, S.M.; Bloom, A.D.; Resnick, M.; Margolin, B.H.; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

30. Galloway, S.M.; Armstrong, M.J.; Reuben, C.; Colman, S.; Brown, B.; Cannon, C.; Bloom, A.D.; Nakamura, F.; Ahmed, M.; Duk, S.; Rimpo, J.; Margolin, B.H.; Resnick, M.A.; Anderson, B.; Zeiger, E. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Molec. Mutagen. 10(Suppl. 10):1-175.

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

32. Hagan, E.C.; Hansen, W.H.; Fitzhugh, O.G.; Jenner, P.M.; Jones, W.I.; Taylor, J.M.; Long, E.L.; Nelson, A.A.; Brouwer, J.B. (1967) Food flavourings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5:141-157.

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

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

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

36. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3-142.

V. REFERENCES

37. Hennings, H.; Shores, R.; Wenk, M.L.; Spangler, E.F.; Tarone, R.; Ysupa, S.H. (1983) Malignant conversion of mouse skin tumours is increased by tumour initiators and unaffected by tumour promoters. Nature 304:67-69.

38. Hjorth, N. (1961) Eczematous Allergy to Balsams. Aarhuus Stiftsbogtrykkerie. Munksgaard. Copenhagen, p. 96.

39. Honecker, H. (1975) CNS (central nervous system)--Availability of amphetamine from amphetaminil. Int. J. Clin. Pharmacol. Biopharm. 12:121. Cited in Opdyke, D.L.J. (1976) Fragrance raw materials monographs: Benzaldehyde. Food Cosmet. Toxicol. 14:693-698.

40. Ishidate, M., Jr.; Sofuni, T.; Yoshikawa, K.; Hayashi, M.; Nohmi, T.; Sawada, M.; Matsuoka, A. (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem. Toxicol. 22:623-636.

41. Jansson, T.; Curvall, M.; Hedin, A.; Enzell, C.R. (1988) In vitro studies of the biological effects of cigarette smoke condensate. III. Induction of SCE by some phenolic and related constituents derived from cigarette smoke. A study of structure-activity relationships. Mutat. Res. 206:17-24.

42. Jenner, P.M.; Hagan, E.C.; Taylor, J.M.; Cook, E.L.; Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. Food Cosmet. Toxicol. 2:327-343.

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

44. Kasamaki, A.; Takahashi, H.; Tsumura, N.; Niwa, J.; Fujita, T.; Urasawa, S. (1982) Genotoxicity of flavoring agents. Mutat. Res. 105: 387-392.

45. Kleeberg, J. (1959) Pharmacological and clinical studies on almonds. Inhibition of peptic activity by benzaldehyde. Arch. Int. Pharmacodyn. Ther. 120:152.

46. Kligman, A.M. (1966) The identification of contact allergens by human assay. III. The maximization test. A procedure for screening and rating contact sensitizers. J. Invest. Derm. 47:393.

47. Kluwe, W.M.; Montgomery, C.A.; Giles, H.D.; Prejean, J.D. (1983) Encephalopathy in rats and nephropathy in rats and mice after subchronic oral exposure to benzaldehyde. Food Chem. Toxicol. 21:245-250.

48. Kochi, M.; Takeuchi, S.; Mizutani, T.; Mochizuki, K.; Matsumoto, Y.; Saito, Y. (1980) Antitumor activity of benzaldehyde. Cancer Treat. Rep. 64:21-23.

49. Laham, S.; Potvin, M. (1987) Biological conversion of benzaldehyde to benzylmercapturic acid in the Sprague-Dawley rat. Drug Chem. Toxicol. 10:209-225.

50. Laham, S.; Potvin, M.; Robinet, M. (1988) Metabolism of benzaldehyde in New Zealand white rabbits. Chemosphere 17:517-524.

51. MacEwen, E.G. (1986) Anti-tumor evaluation of benzaldehyde in the dog and cat. Am. J. Vet. Res. 47:451-452.

52. Macht, D.I. (1922) A pharmacological examination of benzaldehyde and mandelic acid. Arch. Int. Pharmacodyn. Ther. 27:163-174.

53. Margolin, B.H.; Collings, B.J.; Mason, J.M. (1983) Statistical analysis and sample-size determinations for mutagenicity experiments with binomial responses. Environ. Mutagen. 5:705-716.

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

55. McConnell, E.E. (1983a) Pathology requirements for rodent two-year studies. I. A review of current procedures. Toxicol. Pathol. 11:60-64.

56. McConnell, E.E. (1983b) Pathology requirements for rodent two-year studies. II. Alternative approaches. Toxicol. Pathol. 11:65-76.

57. McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76: 283-289.

58. McGregor, D.B.; Brown, A.; Howgate, S.; McBride, D.; Riach, C.; Caspary, W.J. (1990) Responses of the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay. IV. 27 coded chemicals. Environ. Molec. Mutagen. (in press).

59. McKnight, B.; Crowley, J. (1984) Tests for differences in tumor incidence based on animal carcinogenesis experiments. J. Am. Stat. Assoc. 79:639-648.

60. The Merck Index (1983) 10th ed. Rahway, NJ: Merck & Co., Inc., p. 150.

61. Milvy, P.; Garro, A.J. (1976) Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite. Mutat. Res. 40: 15-18.

62. Moreno, O.M. (1973). Report to RIFM, 23 July. Cited in Opdyke, D.L.J. (1976) Fragrance raw materials monographs: Benzaldehyde. Food Cosmet. Toxicol. 14:693-698.

63. Mortelmans, K.; Haworth, S.; Lawlor, T.; Speck, W.; Tainer, B.; Zeiger, E. (1986) Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. Environ. Mutagen. 8(Suppl. 7):1-119.

64. Myhr, B.; Bowers, L.; Caspary, W.J. (1985) Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. Prog. Mutat. Res. 5:555-568.

65. Nambata, T.; Terada, N.; Mizutani, T.; Takeuchi, S. (1982) Characteristics of C3H/He mouse embryo cell lines established by culture with or without benzaldehyde. Gann 73:592-599.

66. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD. 65 p.

67. National Cancer Institute (NCI) (1978) Bioassay of Dibromochloropropane for Possible Carcinogenicity. NCI Technical Report No. 28. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

68. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

69. National Toxicology Program (NTP) (1986a) Toxicology and Carcinogenesis Studies of Benzyl Acetate in F344/N Rats and $B6C3F_1$ Mice. NTP Technical Report No. 250. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 204 p.

70. National Toxicology Program (NTP) (1986b) Toxicology and Carcinogenesis Studies of Diglycidyl Resorcinol Ether in F344/N Rats and $B6C3F_1$ Mice. NTP Technical Report No. 257. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. 222 p.

71. National Toxicology Program (NTP) (1986c) Carcinogenesis Studies of Ethyl Acrylate in F344/N Rats and $B6C3F_1$ Mice. NTP Technical Report No. 259. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 224 p.

72. National Toxicology Program (NTP) (1986d) Toxicology and Carcinogenesis Studies of 3-Chloro-2-Methylpropene in F344/N Rats and $B6C3F_1$ Mice. NTP Technical Report No. 300. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 196 p.

73. National Toxicology Program (NTP) (1986e) Toxicology and Carcinogenesis Studies of Dimethylvinyl Chloride (1-Chloro-2-Methylpropene) in F344/N Rats and $B6C3F_1$ Mice. NTP Technical Report No. 316. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 238 p.

V. REFERENCES

74. National Toxicology Program (NTP) (1989a) Toxicology and Carcinogenesis Studies of Benzyl Alcohol in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 343. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 158 p.

75. National Toxicology Program (NTP) (1989b) Toxicology and Carcinogenesis Studies of Dichlorvos in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 342. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 208 p.

76. Nohmi, T.; Miyata, R.; Yoshikawa, K.; Ishidate, M., Jr. (1985) Mutagenicity tests on organic chemical contaminants in city water and related compounds. I. Bacterial mutagenicity tests. Eisei Shikenjo Hokoku 103:60-64.

77. Odashima, S. (1979) Tumours of the oral cavity, pharynx, oesophagus and stomach. Pathology of Tumours of Laboratory Animals, Vol. II: Tumours of the Mouse. Lyon, France: International Agency for Research on Cancer.

78. Opdyke, D.L.J. (1976) Fragrance raw materials monographs: Benzaldehyde. Food Cosmet. Toxicol. 14:693-698.

79. Osol, A., Ed. (1980) Remington's Pharmaceutical Sciences. Easton, PA: Mack Publishing Company. 1928 p.

80. Pettersen, E.O.; Nome, O.; Ronning, O.W.; Oftebro, R. (1983) Effects of benzaldehyde on survival and cell-cycle kinetics of human cells cultivated *in vitro*. Eur. J. Cancer Clin. Oncol. 19:507-514.

81. Robertson, J.S.; Dunstan, P.J. (1972) Metabolism of hydroanthracenones in rabbits. Biochem. J. 127:119-123.

82. Sadtler Standard Spectra. IR No. 3010; NMR No. 17861M. Philadelphia: Sadtler Research Laboratories.

83. Schweinsberg, F.; Danecki, S.; Grotzke, J.; von Karsa, L.; Burkle, V. (1986) Modifying effects of disulfiram on DNA adduct formation and persistence of benzaldehyde in N-nitroso-N-methyl-benzylamine-induced carcinogenesis in rats. J. Cancer Res. Clin. Oncol. 112:75-80.

84. Shackelford, W.M.; Keith, L.H. (1976) Frequency of Organic Compounds Identified in Water. Athens, GA: U.S. Environmental Protection Agency.

85. Simmon, V.F.; Kauhanen, K. (1978) *In vitro* Microbiological Mutagenicity Assays of Benzoic Acid. Report No. LSU-5612. Menlo Park, CA: SRI International. 14 p.

86. Taetle, R.; Howell, S.B. (1983) Preclinical reevaluation of benzaldehyde as a chemotherapeutic agent. Cancer Treat. Rep. 67:561-566.

87. Takeuchi, S.; Kochi, M.; Sakaguchi, K.; Nakagawa, K.; Mizutani, T. (1978) Benzaldehyde as a carcinostatic principle in figs. Agric. Biol. Chem. 42:1449-1451.

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

89. Teuchy, H.; Quatacker, J.; Wolf, G.; Van Sumere, C.F. (1971) Quantitative investigation of the hippuric acid formation in the rat after administration of some possible aromatic and hydroaromatic precursors. Arch. Int. Physiol. Biochim. 79:573-587.

90. Thomas, K.-H. (1958) Pharmakologie der atherischen Ole. Parfuem. Kosmet. 39:766.

91. Verschueren, K. (1977) Handbook of Environmental Data on Organic Chemicals. New York: Van Nostrand Reinhold Company, pp. 111-113.

92. Vogel, A.I. (1959) Practical Organic Chemistry, 3rd ed. London: Longmans, p. 693.

93. Williams, A.E. (1978). Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 3. New York: John Wiley & Sons, Inc., pp. 736-743.

94. Woodruff, R.C.; Mason, J.M.; Valencia, R.; Zimmering, S. (1985) Chemical mutagenesis testing in Drosophila. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mol. Mutagen. 7:667-702.

95. Zlatkis, A.; Liebich, H.M. (1971) Profile of volatile metabolites in human urine. Clin. Chem. 17:592-594.

96. Zundel, J.-L.; Miyakawa, T.; Sakaguchi, K. (1978) Derivatives and analogues of benzaldehyde selectively cytotoxic to SV-40 transformed cells. Agric. Biol. Chem. 42:2191-2193.

APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

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

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(47)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Intestine large, cecum	(49)	(48)	(47)
Fibrosarcoma	1 (2%)		
Leukemia mononuclear		1 (2%)	
Intestine small, jejunum	(49)	(50)	(48)
Schwannoma malignant	1 (2%)		
Liver	(50)	(50)	(50)
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Fibrous histiocytoma		1 (2%)	
Hepatocellular carcinoma		1 (2%)	
Leukemia mononuclear	10 (20%)	17 (34%)	14 (28%)
Lymphoma malignant lymphocytic			1 (2%)
Neoplastic nodule	2 (4%)		1 (2%)
Mesentery	*(50)	*(50)	*(50)
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Leukemia mononuclear		1 (2%)	
Liposarcoma	1 (2%)		
Mesothelioma malignant		5 (10%)	2 (4%)
Pancreas	(49)	(49)	(48)
Adenoma	3 (6%)	2 (4%)	7 (15%)
Leukemia mononuclear	2 (4%)	3 (6%)	
Lymphoma malignant lymphocytic			1 (2%)
Pharynx	*(50)	*(50)	*(50)
Papilloma squamous			1 (2%)
Salivary glands	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin	1 (2%)		1 (2%)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Stomach, glandular	(50)	(50)	(50)
Carcinoma			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	2 (4%)	3 (6%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Squamous cell carcinoma, metastatic, Zymbal gland			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Carcinoma			1 (2%)
Leukemia mononuclear	6 (12%)	4 (8%)	4 (8%)

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

	Vehicle Control	200 mg/kg	400 mg/kg
ENDOCRINE SYSTEM (Continued)			
Adrenal gland, medulla	(49)	(50)	(49)
Leukemia mononuclear	4 (8%)	3 (6%)	2 (4%)
Pheochromocytoma malignant	2 (4%)	5 (10%)	5 (10%)
Pheochromocytoma benign	14 (29%)	16 (32%)	13 (27%)
Bilateral, pheochromocytoma benign	3 (6%)	3 (6%)	1 (2%)
Islets, pancreatic	(49)	(48)	(48)
Adenoma	4 (8%)	8 (17%)	1 (2%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(49)	(50)	(49)
Adenoma	15 (31%)	22 (44%)	11 (22%)
Carcinoma	3 (6%)		3 (6%)
Carcinoma, metastatic, preputial gland		1 (2%)	
Leukemia mononuclear	3 (6%)		2 (4%)
Thyroid gland	(50)	(50)	(49)
C-cell, adenoma	4 (8%)	8 (16%)	7 (14%)
C-cell, carcinoma	1 (2%)	2 (4%)	1 (2%)
Follicular cell, adenoma		2 (4%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Preputial gland	(50)	(50)	(50)
Adenoma	1 (2%)	3 (6%)	3 (6%)
Carcinoma	1 (2%)	4 (8%)	4 (8%)
Prostate	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Seminal vesicle	*(50)	*(50)	*(50)
Carcinoma, metastatic, uncertain primary site		1 (2%)	
Testes	(50)	(50)	(49)
Bilateral, interstitial cell, adenoma	40 (80%)	38 (76%)	24 (49%)
Interstitial cell, adenoma	6 (12%)	9 (18%)	7 (14%)
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Bone marrow	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear	4 (8%)	4 (8%)	4 (8%)
Lymph node	(50)	(50)	(50)
Axillary, lymphoma malignant lymphocytic			1 (2%)
Mediastinal, leukemia mononuclear	3 (6%)	1 (2%)	1 (2%)
Mediastinal, mesothelioma malignant, metastatic, mesentery			1 (2%)
Pancreatic, leukemia mononuclear		1 (2%)	1 (2%)
Renal, lymphoma malignant lymphocytic			1 (2%)
Lymph node, mandibular	(49)	(48)	(46)
Carcinoma, metastatic, thyroid gland		1 (2%)	1 (2%)
Leukemia mononuclear	4 (8%)	4 (8%)	5 (11%)
Lymphoma malignant lymphocytic			1 (2%)
Lymph node, mesenteric	(50)	(49)	(48)
Leukemia mononuclear	3 (6%)	4 (8%)	4 (8%)
Lymphoma malignant lymphocytic			1 (2%)

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

	Vehicle Control	200 mg/kg	400 mg/kg
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Leiomyosarcoma	1 (2%)		
Leukemia mononuclear	10 (20%)	17 (34%)	15 (30%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Schwannoma malignant		1 (2%)	
Thymus	(47)	(30)	(49)
Leukemia mononuclear		1 (3%)	
Lymphoma malignant lymphocytic			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(47)	(44)
Adenoma		1 (2%)	
Carcinoma	1 (2%)		
Fibroadenoma	3 (6%)	2 (4%)	1 (2%)
Skin	(50)	(49)	(50)
Basal cell carcinoma		2 (4%)	
Keratoacanthoma	1 (2%)		4 (8%)
Papilloma		1 (2%)	3 (6%)
Sebaceous gland, carcinoma		1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	3 (6%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)	2 (4%)
Subcutaneous tissue, fibrous histiocytoma			1 (2%)
Subcutaneous tissue, lipoma		1 (2%)	
Subcutaneous tissue, liposarcoma		1 (2%)	
Subcutaneous tissue, myxosarcoma		2 (4%)	
Subcutaneous tissue, sarcoma		1 (2%)	
Subcutaneous tissue, schwannoma benign	1 (2%)		
Subcutaneous tissue, schwannoma malignant	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Osteosarcoma			1 (2%)
Skeletal muscle	*(50)	*(50)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Carcinoma, metastatic, thyroid gland		1 (2%)	
Hemangiosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Carcinoma, metastatic, preputial gland		1 (2%)	
Granular cell tumor benign	1 (2%)		1 (2%)
Leukemia mononuclear	1 (2%)		
Sarcoma, metastatic, skin		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	
Carcinoma, metastatic, preputial gland		1 (2%)	
Carcinoma, metastatic, thyroid gland		1 (2%)	1 (2%)
Carcinoma, metastatic, uncertain primary site		1 (2%)	

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

	Vehicle Control	200 mg/kg	400 mg/kg
RESPIRATORY SYSTEM			
Lung (Continued)	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	6 (12%)	8 (16%)
Lymphoma malignant lymphocytic			1 (2%)
Mesothelioma malignant, metastatic, mesentery			1 (2%)
Squamous cell carcinoma, metastatic, Zymbal gland			1 (2%)
Nose	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	1 (2%)
Trachea	(50)	(50)	(50)
Leukemia mononuclear			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Squamous cell carcinoma	1 (2%)		2 (4%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	5 (10%)	6 (12%)	6 (12%)
Lymphoma malignant lymphocytic			1 (2%)
Urinary bladder	(49)	(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	10 (20%)	17 (34%)	16 (32%)
Mesothelioma malignant		5 (10%)	2 (4%)
Hemangiosarcoma		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant histiocytic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	37	29	21
Moribund	10	12	17
Dead	3	9	12
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	50	42
Total primary neoplasms	133	170	133
Total animals with benign neoplasms	48	49	38
Total benign neoplasms	104	121	90
Total animals with malignant neoplasms	24	34	33
Total malignant neoplasms	29	49	43
Total animals with secondary neoplasms ***	3	4	4
Total secondary neoplasms	5	12	7
Total animals with malignant neoplasms Uncertain primary site		1	

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

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

WEEKS ON STUDY	069	073	073	084	084	085	085	086	088	100	104	104	104	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	061	071	101	051	081	041	082	062	052	102	031	053	091	111	112	113	114	222	223	224	225	115	121	332	333
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant		X																							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X								X		X					X							
Neoplastic nodule																X									
Mesentery							+	+		+															
Liposarcoma								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+																		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Leukemia mononuclear											X							X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Pheochromocytoma malignant														X								X			
Pheochromocytoma benign												X							X	X			X		X
Bilateral, pheochromocytoma benign										X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				X
Carcinoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X	X	X				X	X					X				X		X			
Carcinoma									X																
Leukemia mononuclear											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma													X												
GENERAL BODY SYSTEM																									
None																									

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	034	035	042	043	044	045	054	055	063	064	072	083	092	065	073	074	075	084	085	093	094	095	103	104	105	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar carcinoma, metastatic, lung																							X			1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma	X																									1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X									X	X		X	X	X						10
Neoplastic nodule									X																	2
Mesentery	+	+	+			+	+	+				+	+	+	+					+			+		+	16
Liposarcoma																										1
Pancreas	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X							X						X									3
Leukemia mononuclear																		X								2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X												X								2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Leukemia mononuclear						X										X		X	X							6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X										X		X								4
Pheochromocytoma malignant																										2
Pheochromocytoma benign		X									X		X			X	X	X		X	X				X	14
Bilateral, pheochromocytoma benign						X	X																			3
Islets, pancreatic	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																		X	4
Carcinoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X	X				X		X			X		X					X				15
Carcinoma				X															X							3
Leukemia mononuclear						X										X										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X													X			X		X		4
C-cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										

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

WEEKS ON STUDY	069	073	073	084	084	085	085	086	088	100	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	061	071	101	051	081	041	082	062	052	102	031	053	091	111	112	113	114	022	023	024	025	015	021	032	033
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Carcinoma		X																							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X				X			X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Interstitial cell, adenoma				X				X												X					
HEMATOPOIETIC SYSTEM																									
Blood																									
Leukemia mononuclear																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear											X														
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X								X														
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																		X							
Leukemia mononuclear			X								X		X					X							
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	M	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Carcinoma																X									
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, fibroma													X									X	X		
Subcutaneous tissue, fibrosarcoma				X									X												
Subcutaneous tissue, schwannoma benign			X																						
Subcutaneous tissue, schwannoma malignant																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Leukemia mononuclear			X																						
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma							X																		
Leukemia mononuclear			X								X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear			M																						
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland	+																								
Squamous cell carcinoma	X																								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	0344	0355	0402	0433	0444	0455	0544	0555	0633	0644	0722	0833	0922	0655	0733	0744	0755	0844	0855	0933	0944	0955	1003	1044	1055		TISSUES TUMORS
GENITAL SYSTEM																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma																											1
Carcinoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma, metastatic, lung																											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		40
Interstitial cell, adenoma						X	X																X				6
HEMATOPOIETIC SYSTEM																											
Blood																+											1
Leukemia mononuclear																X											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear						X										X		X									4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Mediastinal, leukemia mononuclear																X		X									3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear						X										X		X									4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																X											3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leiomyosarcoma																											1
Leukemia mononuclear						X									X	X		X	X	X							10
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		47
Carcinoma																											1
Fibroadenoma											X	X															3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Keratoacanthoma							X																				1
Subcutaneous tissue, fibroma													X					X									5
Subcutaneous tissue, fibrosarcoma																											2
Subcutaneous tissue, schwannoma benign																											1
Subcutaneous tissue, schwannoma malignant					X																						1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle																											1
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Granular cell tumor benign																									X		1
Leukemia mononuclear																											1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar carcinoma																							X				2
Leukemia mononuclear						X									X	X		X	X								7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSES SYSTEM																											
Ear																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Zymbal gland																											1
Squamous cell carcinoma																											1
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear						X										X		X	X								5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		49

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 200 mg/kg

WEEKS ON STUDY	034	071	081	081	089	091	094	096	096	097	098	099	100	102	102	102	102	102	103	104	104	105	105	105	105
CARCASS ID	241	271	221	231	281	292	232	211	261	222	251	301	212	282	252	293	262	291	223	283	224	213	214	215	225
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																		X							
Fibrous histiocytoma																			X						
Hepatocellular carcinoma																									X
Leukemia mononuclear						X								X	X					X		X			
Mesentery		+	+	+	+					+			M	+			+	+				+			
Carcinoma, metastatic, uncertain primary site																		X							
Leukemia mononuclear																									
Mesothelioma malignant										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																X									
Leukemia mononuclear															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel																		+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Leukemia mononuclear															X					X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X									X					X					
Pheochromocytoma malignant																		X							
Pheochromocytoma benign				X			X							X			X	X		X	X	X	X		X
Bilateral, pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	A	+	+	+	+	+	+	+	+
Adenoma												X				X		X			X		X		
Carcinoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X		X							X		X	X		X	X	X	X			X		X
Carcinoma, metastatic, preputial gland																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X		X			X	X					X		X
C-cell, carcinoma																			X						
Follicular cell, adenoma											X														
GENERAL BODY SYSTEM																									
Tissue, NOS									+																
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X						X	
Carcinoma		X		X														X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site																		X							
Leukemia mononuclear															X										
Seminal vesicle																	+	+							
Carcinoma, metastatic, uncertain primary site																		X							
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			X	X				X				X			X					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	233	234	235	242	243	244	245	253	254	255	263	264	265	272	273	274	275	284	285	294	295	302	303	304	305	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																X										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Fibrous histiocytoma																										1
Hepatocellular carcinoma																										1
Leukemia mononuclear				X	X				X		X		X	X	X	X	X			X				X	X	17
Mesentery				+	+		+	+		+	+			+		+		+		+		+	+		+	22
Carcinoma, metastatic, uncertain primary site																										1
Leukemia mononuclear																X										1
Mesothelioma malignant							X	X		X													X			5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		2
Leukemia mononuclear				X												X										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																						1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X												X										3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear				X							X															4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Pheochromocytoma malignant											X					X						X	X			5
Pheochromocytoma benign				X						X		X								X				X	X	16
Bilateral, pheochromocytoma benign			X		X																					3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X										X													X		8
Carcinoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X	X	X		X	X			X	X					X	X		X		X				22
Carcinoma, metastatic, preputial gland																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell, adenoma	X										X															8
C cell, carcinoma																				X						2
Follicular cell, adenoma											X															2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															3
Carcinoma																						X				4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Leukemia mononuclear																										1
Seminal vesicle																										2
Carcinoma, metastatic, uncertain primary site																										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	X	38
Interstitial cell, adenoma												X						X								9

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	034	071	081	081	089	091	094	096	096	097	098	099	100	102	102	102	102	102	103	104	104	105	105	105	105
CARCASS ID	241	271	221	231	281	292	232	211	261	222	251	301	212	282	252	293	262	291	223	283	224	213	214	215	225
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																			X						
Leukemia mononuclear															X					X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear															X										
Pancreatic, leukemia mononuclear															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																			X						
Leukemia mononuclear						X									X					X					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear															X					X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leukemia mononuclear						X								X	X					X		X			
Schwannoma malignant														X											
Thymus	+	+	M	M	+	+	+	+	+	+	M	M	M	M	+	+	+	+	M	+	M	+	M	M	+
Leukemia mononuclear															X										
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Fibroadenoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Papilloma											X														
Sebaceous gland, carcinoma																									X
Subcutaneous tissue, fibroma										X													X		
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma						X																			
Subcutaneous tissue, liposarcoma																									
Subcutaneous tissue, myxosarcoma	X											X													
Subcutaneous tissue, sarcoma											X														
Subcutaneous tissue, schwannoma malignant								X																	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+	+									+						
Carcinoma, metastatic, thyroid gland																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, preputial gland																									
Sarcoma, metastatic, skin											X														
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, preputial gland																									
Carcinoma, metastatic, thyroid gland																			X						
Carcinoma, metastatic, uncertain primary site																		X							
Leukemia mononuclear						X									X					X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X					X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	233	234	235	242	243	244	245	253	254	255	263	264	265	272	273	274	275	284	285	294	295	302	303	304	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Leukemia mononuclear																X				X						4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear																										1
Pancreatic, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear																X										4
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X												X										4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Leukemia mononuclear				X	X			X		X		X	X	X	X	X				X				X	X	17
Schwannoma malignant																										1
Thymus	M	M	M	M	+	M	+	+	M	M	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	30
Leukemia mononuclear																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Fibroadenoma																				X						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Basal cell carcinoma							X																X			2
Papilloma																										1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma																		X								3
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, liposarcoma			X																							1
Subcutaneous tissue, myxosarcoma																										2
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle				+																						4
Carcinoma, metastatic, thyroid gland																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, preputial gland																						X				1
Sarcoma, metastatic, skin																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
Alveolar/bronchiolar carcinoma																							X			1
Carcinoma, metastatic, preputial gland																						X				1
Carcinoma, metastatic, thyroid gland																										1
Carcinoma, metastatic, uncertain primary site																										1
Leukemia mononuclear				X												X				X						6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X											X				X						6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 400 mg/kg

WEEKS ON STUDY	022	029	038	043	054	054	054	056	061	064	072	073	074	080	080	080	082	084	085	087	090	098	098	100	101
CARCASS ID	201	154	161	111	191	202	192	121	131	193	151	132	181	112	122	194	141	171	142	133	152	134	135	172	162
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	M	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X			X							X		X	
Lymphoma malignant lymphocytic																						X			
Neoplastic nodule																									
Mesentery								+	+	+						+									
Mesothelioma malignant																X									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																							X		
Lymphoma malignant lymphocytic																						X			
Pharynx																									
Papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																							X		
Lymphoma malignant lymphocytic																						X			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Lymphoma malignant lymphocytic																						X			
CARDIOVASCULAR SYSTEM																									
Blood vessel																+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymphoma malignant lymphocytic																						X			
Squamous cell carcinoma, metastatic, Zymbal gland																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Carcinoma																									
Leukemia mononuclear														X							X				
Adrenal gland, medulla	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Pheochromocytoma malignant											X												X		
Pheochromocytoma benign																X				X	X	X			
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																						X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X	X												X
Carcinoma																							X	X	
Leukemia mononuclear														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
C-cell, adenoma																				X				X	
C-cell, carcinoma												X													
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Penis																				+					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma									X				X		X										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X			
Seminal vesicle																								+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Bilateral, interstitial cell, adenoma																			X		X	X	X	X	
Interstitial cell, adenoma																X		X							

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	102	103	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	203	143	144	173	113	114	115	123	124	125	145	153	155	163	164	165	174	175	182	183	184	185	195	204	205	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X		X		X			X		X			X			X				X	14
Lymphoma malignant lymphocytic																										1
Neoplastic nodule							X																			1
Mesentery		+			+	+	+	+	+	+	+	+					+	+			+	+	+	+		19
Mesothelioma malignant											X															2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma						X						X						X		X		X	X			7
Lymphoma malignant lymphocytic																										1
Pharynx																						+				1
Papilloma squamous																						X				1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, skin																										1
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																X										1
Lymphoma malignant lymphocytic																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																						1
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma, metastatic, Zymbal gland	X																									1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																						X				1
Leukemia mononuclear				X				X																		4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X																						2
Pheochromocytoma malignant	X						X										X									5
Pheochromocytoma benign			X	X	X	X			X		X							X		X					X	13
Bilateral, pheochromocytoma benign																								X		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																		X								1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	49
Adenoma	X	X			X				X								X		X				X	X		11
Carcinoma																		X								3
Leukemia mononuclear				X																						2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma									X				X		X		X					X				7
C-cell, carcinoma																										1
Follicular cell, adenoma																	X									1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X										X								3
Carcinoma																			X							4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Seminal vesicle																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma				X	X	X	X	X	X	X	X	X		X	X	X		X	X		X	X	X	X	X	24
Interstitial cell, adenoma	X		X										X				X			X						7

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	022	029	038	043	054	054	054	056	061	064	072	073	074	080	080	080	082	084	085	087	090	098	098	100	101
CARCASS ID	201	154	161	111	191	202	192	121	131	193	151	132	181	112	122	194	141	171	142	133	152	134	135	172	162
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X									X							X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant lymphocytic																						X			
Mediastinal, leukemia mononuclear					X																				
Mediastinal, mesothelioma malignant, metastatic, mesentery																X									
Pancreatic, leukemia mononuclear																					X				
Renal, lymphoma malignant lymphocytic																						X			
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland												X													
Leukemia mononuclear					X						X			X							X				
Lymphoma malignant lymphocytic																						X			
Lymph node, mesenteric		+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X									X											
Lymphoma malignant lymphocytic																						X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X			X							X				
Lymphoma malignant histiocytic																								X	
Lymphoma malignant lymphocytic																						X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X			
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
Papilloma									X																
Subcutaneous tissue, fibroma																								X	
Subcutaneous tissue, fibrosarcoma																							X	X	
Subcutaneous tissue, fibrous histiocytoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																			X						
Skeletal muscle																				+					
Hemangiosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																			X						
Peripheral nerve	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland												X													
Leukemia mononuclear					X						X			X							X				
Lymphoma malignant lymphocytic																						X			
Mesothelioma malignant, metastatic, mesentery																X									
Squamous cell carcinoma, metastatic, Zymbal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymphoma malignant lymphocytic																						X			
SPECIAL SENSES SYSTEM																									
Ear														+											
Eye	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	I	+	+	+	+	M
Zymbal gland																									
Squamous cell carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X			X											
Lymphoma malignant lymphocytic																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																						X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	102	103	103	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	203	143	144	173	113	114	115	123	124	125	145	153	155	163	164	165	174	175	182	183	184	185	195	204	205	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X																						4
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant lymphocytic																										1
Mediastinal, leukemia mononuclear																										1
Mediastinal, mesothelioma malignant, metastatic, mesentery																										1
Pancreatic, leukemia mononuclear																										1
Renal, lymphoma malig. lymphocytic																										1
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear				X																						5
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear				X														X								4
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X		X		X		X		X	X		X			X		X	X				X	15
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Fibroadenoma							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma													X									X	X			4
Papilloma			X				X																			3
Subcutaneous tissue, fibroma								X														X				3
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, fibrous histiocytoma			X																							1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle										+								+								3
Hemangiosarcoma																		X								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Leukemia mononuclear				X									X					X							X	8
Lymphoma malignant lymphocytic																										1
Mesothelioma malignant, metastatic, mesentery																										1
Squamous cell carcinoma, metastatic, Zymbal gland	X																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								1
Lymphoma malignant lymphocytic																										1
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Zymbal gland	+	+																								2
Squamous cell carcinoma	X	X																								2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X														X							X	6
Lymphoma malignant lymphocytic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	17/49 (35%)	19/50 (38%)	14/49 (29%)
Adjusted Rates (b)	44.5%	50.4%	50.3%
Terminal Rates (c)	15/36 (42%)	11/29 (38%)	8/21 (38%)
Day of First Observation	696	564	558
Life Table Tests (d)	P=0.164	P=0.193	P=0.208
Logistic Regression Tests (d)	P=0.403	P=0.433	P=0.439
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test (d)		P=0.447	P=0.332N
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	2/49 (4%)	5/50 (10%)	5/49 (10%)
Adjusted Rates (b)	5.6%	16.3%	18.2%
Terminal Rates (c)	2/36 (6%)	4/29 (14%)	2/21 (10%)
Day of First Observation	729	714	499
Life Table Tests (d)	P=0.051	P=0.142	P=0.080
Logistic Regression Tests (d)	P=0.097	P=0.177	P=0.149
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.226	P=0.218
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	19/49 (39%)	23/50 (46%)	19/49 (39%)
Adjusted Rates (b)	49.8%	61.5%	62.1%
Terminal Rates (c)	17/36 (47%)	15/29 (52%)	10/21 (48%)
Day of First Observation	696	564	499
Life Table Tests (d)	P=0.031	P=0.085	P=0.046
Logistic Regression Tests (d)	P=0.140	P=0.277	P=0.172
Cochran-Armitage Trend Test (d)	P=0.541N		
Fisher Exact Test (d)		P=0.300	P=0.582N
Preputial Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	2.2%	9.6%	12.4%
Terminal Rates (c)	0/37 (0%)	2/29 (7%)	2/21 (10%)
Day of First Observation	588	714	593
Life Table Tests (d)	P=0.104	P=0.252	P=0.163
Logistic Regression Tests (d)	P=0.185	P=0.307	P=0.282
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.309	P=0.309
Preputial Gland: Carcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	2.0%	10.2%	11.9%
Terminal Rates (c)	0/37 (0%)	1/29 (3%)	1/21 (5%)
Day of First Observation	507	495	427
Life Table Tests (d)	P=0.072	P=0.161	P=0.109
Logistic Regression Tests (d)	P=0.339	P=0.213	P=0.364
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.181	P=0.181
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (b)	4.2%	16.6%	23.2%
Terminal Rates (c)	0/37 (0%)	3/29 (10%)	3/21 (14%)
Day of First Observation	507	495	427
Life Table Tests (d)	P=0.017	P=0.109	P=0.028
Logistic Regression Tests (d)	P=0.134	P=0.151	P=0.146
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test (d)		P=0.134	P=0.080

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

	Vehicle Control	200 mg/kg	400 mg/kg
Pancreatic Islets: Adenoma			
Overall Rates (a)	4/49 (8%)	8/48 (17%)	1/48 (2%)
Adjusted Rates (b)	11.1%	23.5%	4.8%
Terminal Rates (c)	4/36 (11%)	4/29 (14%)	1/21 (5%)
Day of First Observation	729	692	729
Life Table Tests (d)	P=0.456N	P=0.105	P=0.371N
Logistic Regression Tests (d)	P=0.371N	P=0.147	P=0.371N
Cochran-Armitage Trend Test (d)	P=0.195N		
Fisher Exact Test (d)		P=0.168	P=0.187N
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	9/48 (19%)	2/48 (4%)
Adjusted Rates (b)	13.9%	26.6%	8.0%
Terminal Rates (c)	5/36 (14%)	5/29 (17%)	1/21 (5%)
Day of First Observation	729	692	680
Life Table Tests (d)	P=0.520N	P=0.108	P=0.460N
Logistic Regression Tests (d)	P=0.417N	P=0.155	P=0.387N
Cochran-Armitage Trend Test (d)	P=0.219N		
Fisher Exact Test (d)		P=0.182	P=0.226N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.9%	5.6%	4.8%
Terminal Rates (c)	2/37 (5%)	1/29 (3%)	1/21 (5%)
Day of First Observation	726	632	729
Life Table Tests (d)	P=0.403N	P=0.578N	P=0.524N
Logistic Regression Tests (d)	P=0.316N	P=0.503N	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (e)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.9%	7.9%	4.8%
Terminal Rates (c)	2/37 (5%)	1/29 (3%)	1/21 (5%)
Day of First Observation	726	632	729
Life Table Tests (d)	P=0.431N	P=0.592	P=0.524N
Logistic Regression Tests (d)	P=0.331N	P=0.661	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661N	P=0.309N
Mammary Gland: Adenoma, Fibroadenoma, or Carcinoma			
Overall Rates (e)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	10.5%	7.9%	4.8%
Terminal Rates (c)	3/37 (8%)	1/29 (3%)	1/21 (5%)
Day of First Observation	726	632	729
Life Table Tests (d)	P=0.297N	P=0.585N	P=0.386N
Logistic Regression Tests (d)	P=0.208N	P=0.503N	P=0.373N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.500N	P=0.181N
Pancreas: Adenoma			
Overall Rates (a)	3/49 (6%)	2/49 (4%)	7/48 (15%)
Adjusted Rates (b)	8.3%	6.2%	31.2%
Terminal Rates (c)	3/36 (8%)	1/29 (3%)	6/21 (29%)
Day of First Observation	729	711	697
Life Table Tests (d)	P=0.018	P=0.590N	P=0.026
Logistic Regression Tests (d)	P=0.024	P=0.532N	P=0.038
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.500N	P=0.150

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

	Vehicle Control	200 mg/kg	400 mg/kg
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	15/49 (31%)	22/50 (44%)	11/49 (22%)
Adjusted Rates (b)	35.7%	57.0%	40.1%
Terminal Rates (c)	10/36 (28%)	13/29 (45%)	6/21 (29%)
Day of First Observation	585	561	506
Life Table Tests (d)	P=0.259	P=0.045	P=0.399
Logistic Regression Tests (d)	P=0.473N	P=0.117	P=0.450N
Cochran-Armitage Trend Test (d)	P=0.225N		
Fisher Exact Test (d)		P=0.121	P=0.246N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	7.8%	0.0%	11.5%
Terminal Rates (c)	2/36 (6%)	0/29 (0%)	1/21 (5%)
Day of First Observation	610		680
Life Table Tests (d)	P=0.426	P=0.143N	P=0.446
Logistic Regression Tests (d)	P=0.534	P=0.116N	P=0.564
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.117N	P=0.661N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	18/49 (37%)	22/50 (44%)	14/49 (29%)
Adjusted Rates (b)	42.0%	57.0%	48.0%
Terminal Rates (c)	12/36 (33%)	13/29 (45%)	7/21 (33%)
Day of First Observation	585	561	506
Life Table Tests (d)	P=0.217	P=0.128	P=0.308
Logistic Regression Tests (d)	P=0.504N	P=0.292	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.231N		
Fisher Exact Test (d)		P=0.298	P=0.259N
Skin: Keratoacanthoma			
Overall Rates (e)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	2.7%	0.0%	17.0%
Terminal Rates (c)	1/37 (3%)	0/29 (0%)	3/21 (14%)
Day of First Observation	729		593
Life Table Tests (d)	P=0.028	P=0.549N	P=0.061
Logistic Regression Tests (d)	P=0.047	P=0.549N	P=0.104
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
Skin: Papilloma			
Overall Rates (e)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.5%	11.1%
Terminal Rates (c)	0/37 (0%)	0/29 (0%)	1/21 (5%)
Day of First Observation		682	427
Life Table Tests (d)	P=0.028	P=0.495	P=0.059
Logistic Regression Tests (d)	P=0.067	P=0.503	P=0.127
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Subcutaneous Tissue: Fibroma			
Overall Rates (e)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	13.2%	9.2%	12.9%
Terminal Rates (c)	4/37 (11%)	2/29 (7%)	2/21 (10%)
Day of First Observation	726	676	697
Life Table Tests (d)	P=0.561N	P=0.477N	P=0.628
Logistic Regression Tests (d)	P=0.476N	P=0.375N	P=0.602N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.357N	P=0.357N

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

	Vehicle Control	200 mg/kg	400 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (e)	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	15.0%	12.5%	15.9%
Terminal Rates (c)	4/37 (11%)	3/29 (10%)	2/21 (10%)
Day of First Observation	585	676	680
Life Table Tests (d)	P=0.528	P=0.497N	P=0.569
Logistic Regression Tests (d)	P=0.470N	P=0.373N	P=0.561N
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test (d)		P=0.370N	P=0.370N
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Myxosarcoma			
Overall Rates (e)	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	4.7%	10.1%	7.0%
Terminal Rates (c)	0/37 (0%)	1/29 (3%)	0/21 (0%)
Day of First Observation	585	235	680
Life Table Tests (d)	P=0.413	P=0.299	P=0.535
Logistic Regression Tests (d)	P=0.471N	P=0.387	P=0.666
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.339	P=0.691
Subcutaneous Tissue: Fibroma, Fibrosarcoma, Sarcoma, or Myxosarcoma			
Overall Rates (e)	6/50 (12%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	15.0%	18.6%	15.9%
Terminal Rates (c)	4/37 (11%)	3/29 (10%)	2/21 (10%)
Day of First Observation	585	235	680
Life Table Tests (d)	P=0.491	P=0.386	P=0.569
Logistic Regression Tests (d)	P=0.361N	P=0.520	P=0.561N
Cochran-Armitage Trend Test (d)	P=0.318N		
Fisher Exact Test (d)		P=0.500	P=0.370N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	46/50 (92%)	47/50 (94%)	31/49 (63%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	37/37 (100%)	29/29 (100%)	21/21 (100%)
Day of First Observation	507	495	558
Life Table Tests (d)	P=0.135	P=0.045	P=0.187
Logistic Regression Tests (d)	P=0.109N	P=0.480	P=0.198N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.500	P<0.001N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	8/50 (16%)	7/49 (14%)
Adjusted Rates (b)	10.8%	23.1%	29.0%
Terminal Rates (c)	4/37 (11%)	4/29 (14%)	5/21 (24%)
Day of First Observation	729	692	605
Life Table Tests (d)	P=0.041	P=0.103	P=0.055
Logistic Regression Tests (d)	P=0.071	P=0.160	P=0.097
Cochran-Armitage Trend Test (d)	P=0.214		
Fisher Exact Test (d)		P=0.178	P=0.251
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	10/50 (20%)	8/49 (16%)
Adjusted Rates (b)	13.2%	28.5%	30.8%
Terminal Rates (c)	4/37 (11%)	5/29 (17%)	5/21 (24%)
Day of First Observation	726	692	506
Life Table Tests (d)	P=0.039	P=0.067	P=0.057
Logistic Regression Tests (d)	P=0.087	P=0.112	P=0.127
Cochran-Armitage Trend Test (d)	P=0.230		
Fisher Exact Test (d)		P=0.131	P=0.264

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

	Vehicle Control	200 mg/kg	400 mg/kg
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	10/50 (20%)	17/50 (34%)	16/50 (32%)
Adjusted Rates (b)	24.6%	50.6%	56.7%
Terminal Rates (c)	7/37 (19%)	13/29 (45%)	10/21 (48%)
Day of First Observation	508	632	373
Life Table Tests (d)	P=0.003	P=0.026	P=0.006
Logistic Regression Tests (d)	P=0.023	P=0.081	P=0.041
Cochran-Armitage Trend Test (d)	P=0.112		
Fisher Exact Test (d)		P=0.088	P=0.127
All Sites: Mesothelioma			
Overall Rates (e)	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	0.0%	15.9%	7.3%
Terminal Rates (c)	0/37 (0%)	4/29 (14%)	1/21 (5%)
Day of First Observation		676	558
Life Table Tests (d)	P=0.104	P=0.020	P=0.156
Logistic Regression Tests (d)	P=0.167	P=0.031	P=0.233
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.028	P=0.247

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

TABLE A4a. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute		
Ethyl acrylate	0/49	0/49
Allyl isovalerate	1/50	1/50
HC Red No. 3	11/50	11/50
C.I. Acid Orange 3	5/50	6/50
Chlorinated paraffins (C_{23}, 43% chlorine)	6/49	6/49
Chlorinated paraffins (C_{12}, 60% chlorine)	11/50	11/50
Allyl isothiocyanate	(b) 1/50	1/50
Geranyl acetate	0/49	0/49
TOTAL	35/397 (8.8%)	36/397 (9.1%)
SD (c)	9.33%	9.39%
Range (d)		
High	11/50	11/50
Low	0/49	0/49
Overall Historical Incidence		
TOTAL	(e) 104/2,011 (5.2%)	(e,f) 107/2,011 (5.3%)
SD (c)	6.70%	6.73%
Range (d)		
High	14/50	14/50
Low	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; data for the benzyl acetate study have been omitted.
(b) Adenoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes three adenomas, NOS
(f) Includes one adenocarcinoma, NOS

TABLE A4b. HISTORICAL INCIDENCE OF MESOTHELIAL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Mesotheliomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	2/50
Allyl isovalerate	2/50
HC Red No. 3	0/50
C.I. Acid Orange 3	3/50
Chlorinated paraffins (C_{23}, 43% chlorine)	1/50
Chlorinated paraffins (C_{12}, 60% chlorine)	4/50
Allyl isothiocyanate	0/50
Geranyl acetate	2/50
TOTAL	(b) 15/450 (3.3%)
SD (c)	2.65%
Range (d)	
High	4/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 78/2,099 (3.7%)
SD (c)	2.56%
Range (d)	
High	6/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes four malignant mesotheliomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 13 malignant mesotheliomas

TABLE A4c. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	5/50
Allyl isovalerate	1/50
HC Red No. 3	9/50
C.I. Acid Orange 3	10/50
Chlorinated paraffins (C_{23}, 43% chlorine)	9/50
Chlorinated paraffins (C_{12}, 60% chlorine)	7/50
Allyl isothiocyanate	2/50
Geranyl acetate	1/50
TOTAL	45/450 (10.0%)
SD (b)	7.68%
Range (c)	
High	10/50
Low	1/50
Overall Historical Incidence	
TOTAL	361/2,099 (17.2%)
SD (b)	9.04%
Range (c)	
High	22/50
Low	1/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(48)	(47)
Edema		2 (4%)	1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)
Parasite metazoan	5 (10%)	4 (8%)	3 (6%)
Intestine large, colon	(50)	(49)	(48)
Inflammation, granulomatous			1 (2%)
Parasite metazoan	5 (10%)	3 (6%)	3 (6%)
Intestine large, rectum	(49)	(49)	(45)
Mineralization		1 (2%)	
Parasite metazoan	9 (18%)	7 (14%)	4 (9%)
Liver	(50)	(50)	(50)
Angiectasis		4 (8%)	4 (8%)
Basophilic focus	37 (74%)	31 (62%)	20 (40%)
Clear cell focus	15 (30%)	11 (22%)	5 (10%)
Congestion		2 (4%)	1 (2%)
Degeneration, cystic		2 (4%)	1 (2%)
Developmental malformation	7 (14%)	6 (12%)	6 (12%)
Eosinophilic focus		1 (2%)	
Focal cellular change	4 (8%)		4 (8%)
Granuloma	23 (46%)	12 (24%)	1 (2%)
Hematopoietic cell proliferation		6 (12%)	3 (6%)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active	3 (6%)		1 (2%)
Bile duct, cyst multilocular	1 (2%)	1 (2%)	
Bile duct, hyperplasia	47 (94%)	45 (90%)	37 (74%)
Centrilobular, atrophy	2 (4%)	1 (2%)	4 (8%)
Centrilobular, necrosis		4 (8%)	3 (6%)
Hepatocyte, hyperplasia, nodular	3 (6%)	3 (6%)	5 (10%)
Hepatocyte, vacuolization cytoplasmic	15 (30%)	14 (28%)	2 (4%)
Kupffer cell, hyperplasia		4 (8%)	1 (2%)
Kupffer cell, pigmentation		2 (4%)	
Lobules, necrosis	1 (2%)	3 (6%)	2 (4%)
Mesentery	(16)	(22)	(19)
Accessory spleen			1 (5%)
Artery, hypertrophy	2 (13%)		3 (16%)
Artery, inflammation, chronic active	3 (19%)	1 (5%)	6 (32%)
Artery, mineralization		1 (5%)	
Fat, inflammation, granulomatous	3 (19%)	10 (45%)	3 (16%)
Fat, mineralization	8 (50%)	13 (59%)	9 (47%)
Fat, necrosis	12 (75%)	15 (68%)	12 (63%)
Fat, pigmentation		1 (5%)	
Pancreas	(49)	(49)	(48)
Atrophy	10 (20%)	9 (18%)	5 (10%)
Basophilic focus			2 (4%)
Hyperplasia, nodular	6 (12%)	6 (12%)	12 (25%)
Inflammation, chronic	4 (8%)		1 (2%)
Inflammation, granulomatous	1 (2%)		
Salivary glands	(50)	(50)	(49)
Atrophy		2 (4%)	
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, suppurative			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(50)	(50)	(50)
Edema	1 (2%)	3 (6%)	
Erosion			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Mineralization		2 (4%)	1 (2%)
Perforation	1 (2%)		
Ulcer		3 (6%)	1 (2%)
Mucosa, dysplasia	1 (2%)		
Mucosa, hyperplasia	2 (4%)	3 (6%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	
Erosion	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Mineralization	1 (2%)	6 (12%)	3 (6%)
Ulcer	2 (4%)		2 (4%)
Mucosa, dysplasia			1 (2%)
Tongue	(1)		
Hyperkeratosis	1 (100%)		
CARDIOVASCULAR SYSTEM			
Blood vessel		(1)	(1)
Aorta, fibrosis			1 (100%)
Aorta, hemorrhage			1 (100%)
Aorta, inflammation, chronic			1 (100%)
Aorta, mineralization		1 (100%)	
Heart	(50)	(50)	(50)
Cardiomyopathy	37 (74%)	42 (84%)	40 (80%)
Thrombus	2 (4%)	4 (8%)	1 (2%)
Epicardium, fibrosis			1 (2%)
Epicardium, inflammation, chronic	1 (2%)		1 (2%)
Myocardium, inflammation, chronic		2 (4%)	5 (10%)
Myocardium, mineralization		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	4 (8%)	10 (20%)	8 (16%)
Angiectasis	5 (10%)	6 (12%)	1 (2%)
Basophilic focus	2 (4%)		
Clear cell focus	7 (14%)	6 (12%)	7 (14%)
Cyst			1 (2%)
Fibrosis			1 (2%)
Hematopoietic cell proliferation		4 (8%)	
Hyperplasia	2 (4%)	9 (18%)	3 (6%)
Necrosis			1 (2%)
Vacuolization cytoplasmic, diffuse		6 (12%)	4 (8%)
Adrenal gland, medulla	(49)	(50)	(49)
Hyperplasia	2 (4%)	6 (12%)	3 (6%)
Infiltration cellular, mononuclear cell		1 (2%)	
Islets, pancreatic	(49)	(48)	(48)
Hyperplasia	3 (6%)		
Parathyroid gland	(48)	(46)	(46)
Hyperplasia	1 (2%)		
Pituitary gland	(49)	(50)	(49)
Pars distalis, angiectasis	4 (8%)	1 (2%)	
Pars distalis, cyst	1 (2%)	6 (12%)	2 (4%)
Pars distalis, hyperplasia	4 (8%)	10 (20%)	8 (16%)
Pars intermedia, angiectasis		1 (2%)	
Pars intermedia, cyst		2 (4%)	1 (2%)
Pars nervosa, hyperplasia			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(50)	(50)	(49)
Concretion		1 (2%)	
Mineralization		1 (2%)	
Pigmentation	18 (36%)	19 (38%)	10 (20%)
Ultimobranchial cyst		1 (2%)	1 (2%)
C-cell, hyperplasia	7 (14%)	15 (30%)	4 (8%)
Follicle, cyst	2 (4%)	2 (4%)	1 (2%)
Follicular cell, hyperplasia		1 (2%)	
GENERAL BODY SYSTEM			
Tissue, NOS		(1)	
Hemorrhage		1 (100%)	
Infiltration cellular, mononuclear cell		1 (100%)	
GENITAL SYSTEM			
Epididymis	(49)	(50)	(49)
Fibrosis		1 (2%)	
Pigmentation		1 (2%)	
Preputial gland	(50)	(50)	(50)
Ectasia	1 (2%)	4 (8%)	5 (10%)
Hyperplasia		1 (2%)	1 (2%)
Inflammation, chronic	35 (70%)	25 (50%)	25 (50%)
Inflammation, suppurative	4 (8%)	9 (18%)	6 (12%)
Metaplasia, squamous		2 (4%)	
Mineralization			1 (2%)
Necrosis		1 (2%)	
Prostate	(50)	(50)	(50)
Corpora amylacea	2 (4%)	6 (12%)	1 (2%)
Ectasia	1 (2%)		
Fibrosis	4 (8%)	4 (8%)	
Inflammation, chronic	10 (20%)	21 (42%)	5 (10%)
Inflammation, suppurative	20 (40%)	27 (54%)	6 (12%)
Testes	(50)	(50)	(49)
Mineralization	24 (48%)	23 (46%)	11 (22%)
Spermatocele	1 (2%)		
Interstitial cell, hyperplasia	1 (2%)		2 (4%)
Seminiferous tubule, atrophy	2 (4%)	7 (14%)	7 (14%)
HEMATOPOIETIC SYSTEM			
Blood	(1)		
Anemia	1 (100%)		
Leukocytosis	1 (100%)		
Bone marrow	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
Depletion		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)		1 (2%)
Myelofibrosis			1 (2%)
Proliferation		9 (18%)	3 (6%)
Lymph node	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid	1 (2%)		
Mediastinal, erythrophagocytosis	2 (4%)	1 (2%)	
Mediastinal, hemorrhage	1 (2%)	2 (4%)	
Mediastinal, hyperplasia, plasma cell			1 (2%)
Mediastinal, hyperplasia, reticulum cell		1 (2%)	
Mediastinal, infiltration cellular, mast cell		1 (2%)	
Mediastinal, pigmentation		3 (6%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mandibular	(49)	(48)	(46)
Depletion		1 (2%)	
Erythrophagocytosis	1 (2%)	1 (2%)	
Hemorrhage		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, plasma cell	3 (6%)	2 (4%)	5 (11%)
Hyperplasia, reticulum cell		1 (2%)	
Lymphatic, dilatation	5 (10%)	1 (2%)	3 (7%)
Lymph node, mesenteric	(50)	(49)	(48)
Depletion		1 (2%)	
Erythrophagocytosis		2 (4%)	
Hemorrhage	1 (2%)	1 (2%)	3 (6%)
Infiltration cellular, mast cell		2 (4%)	1 (2%)
Pigmentation	38 (76%)	33 (67%)	26 (54%)
Spleen	(50)	(50)	(50)
Congestion		1 (2%)	
Fibrosis	2 (4%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation	6 (12%)	11 (22%)	6 (12%)
Hyperplasia, re cell	1 (2%)	1 (2%)	
Necrosis			1 (2%)
Pigmentation, hemosiderin	1 (2%)	5 (10%)	2 (4%)
Lymphoid follicle, atrophy		2 (4%)	2 (4%)
Red pulp, atrophy		3 (6%)	4 (8%)
Thymus	(47)	(30)	(49)
Cyst	2 (4%)		
Hemorrhage			1 (2%)
Epithelial cell, hyperplasia	1 (2%)	2 (7%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(47)	(47)	(44)
Hyperplasia, cystic	16 (34%)	16 (34%)	7 (16%)
Hyperplasia, lobular	2 (4%)	5 (11%)	1 (2%)
Inflammation, granulomatous		1 (2%)	
Skin	(50)	(49)	(50)
Acanthosis		1 (2%)	
Cyst epithelial inclusion	1 (2%)	6 (12%)	2 (4%)
Cyst multilocular		1 (2%)	
Fibrosis	2 (4%)		
Foreign body		1 (2%)	
Hemorrhage	1 (2%)		
Inflammation, chronic		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)
Mineralization			2 (4%)
Ulcer			2 (4%)
Hair follicle, atrophy		1 (2%)	
Sebaceous gland, ectasia	1 (2%)		
Subcutaneous tissue, edema		1 (2%)	
Subcutaneous tissue, fibrosis	2 (4%)		
Subcutaneous tissue, granuloma		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, hyperostosis		1 (2%)	
Skeletal muscle	(1)	(4)	(3)
Edema		1 (25%)	
Hemorrhage			1 (33%)
Inflammation, chronic			1 (33%)
Inflammation, chronic active		1 (25%)	
Mineralization			1 (33%)
Necrosis			1 (33%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	2 (4%)	2 (4%)	1 (2%)
Corpora amylacea			1 (2%)
Developmental malformation		1 (2%)	
Hemorrhage		2 (4%)	2 (4%)
Hydrocephalus	2 (4%)	1 (2%)	
Inflammation, chronic			1 (2%)
Necrosis			1 (2%)
Peripheral nerve	(49)	(49)	(46)
Infiltration cellular, mast cell		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	
Axon, hypertrophy		2 (4%)	
Spinal cord	(50)	(50)	(50)
Gray matter, cytoplasmic alteration		1 (2%)	
Gray matter, degeneration	1 (2%)	1 (2%)	1 (2%)
Gray matter, necrosis	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Adenomatosis	1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)	4 (8%)	8 (16%)
Foreign body	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)		
Infiltration cellular, histiocytic	18 (36%)	14 (28%)	9 (18%)
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Leukocytosis			1 (2%)
Mineralization	1 (2%)		
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)	4 (8%)
Alveolus, edema	1 (2%)	1 (2%)	3 (6%)
Artery, mediastinum, hypertrophy	1 (2%)		1 (2%)
Artery, mediastinum, inflammation, chronic active	1 (2%)		1 (2%)
Lymphatic, dilatation		1 (2%)	
Mediastinum, edema		1 (2%)	
Nose	(50)	(50)	(50)
Exudate	14 (28%)	9 (18%)	8 (16%)
Foreign body	1 (2%)	3 (6%)	3 (6%)
Fungus	10 (20%)	4 (8%)	2 (4%)
Inflammation, chronic	7 (14%)	3 (6%)	4 (8%)
Mucosa, hyperplasia	3 (6%)	2 (4%)	2 (4%)
Mucosa, metaplasia, squamous	5 (10%)	5 (10%)	2 (4%)
Trachea	(50)	(50)	(50)
Inflammation, chronic		2 (4%)	
Mineralization		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(45)
Cataract	9 (18%)	3 (6%)	10 (22%)
Hemorrhage		1 (2%)	
Cornea, inflammation, chronic		1 (2%)	
Cornea, mineralization	1 (2%)		
Retina, atrophy	31 (62%)	28 (56%)	35 (78%)
Sclera, mineralization	25 (50%)	26 (52%)	20 (44%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Angiectasis		1 (2%)	
Cyst	1 (2%)		
Fibrosis		1 (2%)	
Glomerulosclerosis		1 (2%)	
Hydronephrosis		1 (2%)	1 (2%)
Infarct			3 (6%)
Inflammation, chronic	29 (58%)	30 (60%)	32 (64%)
Inflammation, suppurative	9 (18%)	13 (26%)	13 (26%)
Mineralization	8 (16%)	15 (30%)	10 (20%)
Nephropathy	50 (100%)	49 (98%)	44 (88%)
Capsule, fibrosis	1 (2%)		
Renal tubule, cytoplasmic alteration	1 (2%)		
Renal tubule, degeneration		1 (2%)	
Renal tubule, hyperplasia	1 (2%)		1 (2%)
Renal tubule, necrosis			2 (4%)
Renal tubule, pigmentation		2 (4%)	3 (6%)
Transitional epithelium, hyperplasia	1 (2%)		5 (10%)
Venule, infiltration cellular, histiocytic		1 (2%)	
Venule, pigmentation		1 (2%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Intestine large, colon	(49)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Intestine small, duodenum	(49)	*(50)	(46)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Intestine small, ileum	(48)	*(50)	(44)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Intestine small, jejunum	(48)	*(50)	(47)
Lymphoma malignant lymphocytic	1 (2%)		
Schwannoma malignant		1 (2%)	
Liver	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear	15 (30%)	19 (38%)	18 (36%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Neoplastic nodule	5 (10%)		1 (2%)
Schwannoma malignant	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		
Sarcoma, metastatic, vagina	1 (2%)		
Pancreas	(48)	*(50)	(50)
Adenoma			1 (2%)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Pharynx	*(50)	*(50)	*(50)
Papilloma squamous	1 (2%)		
Salivary glands	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Papilloma squamous			2 (4%)
Stomach, glandular	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	2 (4%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear		1 (2%)	3 (6%)
Lymphoma malignant lymphocytic			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Adenoma		2 (4%)	2 (4%)
Leukemia mononuclear	1 (2%)	4 (8%)	5 (10%)
Lymphoma malignant lymphocytic	1 (2%)		
Adrenal gland, medulla	(49)	(49)	(47)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Pheochromocytoma malignant	2 (4%)		2 (4%)
Pheochromocytoma benign	5 (10%)	2 (4%)	3 (6%)
Bilateral, pheochromocytoma benign		1 (2%)	

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

	Vehicle Control	200 mg/kg	400 mg/kg
ENDOCRINE SYSTEM (Continued)			
Islets, pancreatic	(48)	*(50)	(50)
Adenoma	1 (2%)	2 (4%)	
Pituitary gland	(49)	(49)	(49)
Adenoma	23 (47%)	31 (63%)	15 (31%)
Carcinoma	3 (6%)	2 (4%)	1 (2%)
Leukemia mononuclear	1 (2%)	3 (6%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Pars intermedia, adenoma	1 (2%)		1 (2%)
Thyroid gland	(50)	*(50)	(50)
Leukemia mononuclear			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
C-cell, adenoma	2 (4%)	1 (2%)	3 (6%)
C-cell, carcinoma		1 (2%)	
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma		2 (4%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(45)	(50)	(48)
Adenoma	1 (2%)	3 (6%)	1 (2%)
Basosquamous tumor malignant			1 (2%)
Carcinoma	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Ovary	(49)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Uterus	(49)	*(50)	(50)
Adenoma			1 (2%)
Leukemia mononuclear		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Polyp stromal	12 (24%)	8 (16%)	14 (28%)
Sarcoma stromal	1 (2%)		
Vagina	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
Sarcoma	1 (2%)		
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear			2 (4%)
Bone marrow	(50)	*(50)	(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymph node	(50)	*(50)	(50)
Inguinal, lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Mediastinal, fibrous histiocytoma		1 (2%)	
Mediastinal, leukemia mononuclear	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant lymphocytic			1 (2%)
Lymph node, mandibular	(46)	*(50)	(47)
Leukemia mononuclear			4 (9%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymph node, mesenteric	(48)	*(50)	(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear			3 (6%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)

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

	Vehicle Control	200 mg/kg	400 mg/kg
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Hemangiosarcoma	1 (2%)		
Leukemia mononuclear	14 (28%)	20 (40%)	16 (32%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		
Sarcoma			1 (2%)
Thymus	(47)	*(50)	(46)
Lymphoma malignant lymphocytic	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)	
Carcinoma	1 (2%)		2 (4%)
Fibroadenoma	28 (56%)	28 (56%)	22 (44%)
Leukemia mononuclear		1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Skin	(50)	*(50)	(50)
Leukemia mononuclear			1 (2%)
Papilloma			2 (4%)
Subcutaneous tissue, fibroma		3 (6%)	
Subcutaneous tissue, lipoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)	1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Meningioma malignant	1 (2%)		
Oligodendroglioma malignant	1 (2%)		
Spinal cord	(50)	(50)	(50)
Schwannoma malignant		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)	
Fibrous histiocytoma		1 (2%)	
Leukemia mononuclear	1 (2%)	8 (16%)	10 (20%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Nose	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Trachea	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(49)
Leukemia mononuclear		1 (2%)	1 (2%)

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

	Vehicle Control	200 mg/kg	400 mg/kg
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Leukemia mononuclear	1 (2%)	6 (12%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Urinary bladder	(49)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Sarcoma, metastatic, vagina	1 (2%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	15 (30%)	20 (40%)	18 (36%)
Hemangiosarcoma	1 (2%)		
Lymphoma malignant mixed	1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	13	16	12
Dead	4	1	9
Terminal sacrifice	33	33	29
TUMOR SUMMARY			
Total animals with primary neoplasms **	46	48	43
Total primary neoplasms	111	119	97
Total animals with benign neoplasms	42	46	37
Total benign neoplasms	81	83	69
Total animals with malignant neoplasms	25	27	24
Total malignant neoplasms	30	36	28
Total animals with secondary neoplasms ***	2	2	
Total secondary neoplasms	3	2	

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

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

WEEKS ON STUDY	052	067	075	077	083	083	086	089	097	097	098	100	100	101	102	103	103	105	105	105	105	105	105	105
CARCASS ID	3411	3811	3311	3611	3911	4011	3111	3622	3122	3511	4022	3922	3322	3522	3113	3221	3711	3223	3224	3323	3334	3114	3115	3225
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																			
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																			
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant lymphocytic					X																			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X			X	X	X						X	X		X				
Lymphoma malignant lymphocytic					X																			
Neoplastic nodule																X								
Schwannoma malignant										X														
Mesentery	+		+		+	+		+			+													
Lymphoma malignant lymphocytic					X																			
Sarcoma, metastatic, vagina						X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+
Leukemia mononuclear						X																		
Lymphoma malignant lymphocytic					X																			
Pharynx																								
Papilloma squamous																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																		
Lymphoma malignant lymphocytic					X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																		
Lymphoma malignant lymphocytic					X																			
CARDIOVASCULAR SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																				
Lymphoma malignant lymphocytic					X																			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X		X																		
Pheochromocytoma malignant	X																				X			
Pheochromocytoma benign												X	X				X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma															X									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma		X			X		X	X				X				X			X		X		X	
Carcinoma									X															
Leukemia mononuclear						X																		
Lymphoma malignant lymphocytic					X																			
Pars intermedia, adenoma											X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																								
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma													X											
Lymphoma malignant lymphocytic					X																			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic					X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic					X																			
Polyp stromal	X	X	X	X													X			X				
Sarcoma stromal										X														
Vagina					+	+				+	+				+								+	
Sarcoma						X																		

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	335	342	343	344	345	353	354	355	363	364	365	372	373	374	375	393	394	395	403	404	382	383	384	385	405	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Intestine small, jejunum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X										X	X				X			X				X	15
Lymphoma malignant lymphocytic																										1
Neoplastic nodule											X		X							X					X	5
Schwannoma malignant																										1
Mesentery							+						+	+												9
Lymphoma malignant lymphocytic																										1
Sarcoma, metastatic, vagina																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Pharynx																									+	1
Papilloma squamous																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Pheochromocytoma malignant																										2
Pheochromocytoma benign			X																	X						5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X	X	X	X	X		X	X	X	X				X					X				X	X	X		23
Carcinoma															X		X									3
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																				X	X					2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	M	+	+	+	45
Adenoma														X												1
Carcinoma																										1
Lymphoma malignant lymphocytic																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Polyp stromal			X			X				X						X				X			X			12
Sarcoma stromal																										1
Vagina																+										7
Sarcoma																										1

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

WEEKS ON STUDY	052	067	075	077	083	083	086	089	097	097	098	100	100	101	102	103	103	105	105	105	105	105	105	105	105
CARCASS ID	341	381	331	361	391	401	311	362	312	351	402	392	332	352	313	321	371	322	323	324	333	334	314	315	325
HEMATOPOIETIC SYSTEM																									
Blood													+											+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, lymphoma malignant lymphocytic					X																				
Mediastinal, leukemia mononuclear				X																					
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymph node, mesenteric	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Leukemia mononuclear				X		X			X	X							X	X		X			X		
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed																									
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																									
Fibroadenoma			X				X	X					X		X		X	X		X			X	X	
Lymphoma malignant lymphocytic					X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma					X																				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland									X																
Meningioma malignant															X										
Oligodendroglioma malignant												X													
Peripheral nerve	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					
Lymphoma malignant lymphocytic					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					
Lymphoma malignant lymphocytic					X																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic					X																				
Sarcoma, metastatic, vagina						X																			

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	335	342	343	344	345	353	354	355	363	364	365	372	373	374	375	393	394	395	403	404	382	383	384	385	405		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Blood																											2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Inguinal, lymphoma malignant lymphocytic																											1
Mediastinal, leukemia mononuclear																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I		46
Lymphoma malignant lymphocytic																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymphoma malignant lymphocytic																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											1
Leukemia mononuclear			X										X	X				X			X				X		14
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed			X																								1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		47
Lymphoma malignant lymphocytic																											1
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma																											1
Carcinoma					X																						1
Fibroadenoma	X	X	X	X	X	X		X	X		X		X	X	X	X	X	X	X	X				X			28
Lymphoma malignant lymphocytic																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Subcutaneous tissue, lipoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, pituitary gland																											1
Meningioma malignant																											1
Oligodendroglioma malignant																											1
Peripheral nerve	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+		47
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Lymphoma malignant lymphocytic																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSES SYSTEM																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Lymphoma malignant lymphocytic																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymphoma malignant lymphocytic																											1
Sarcoma, metastatic, vagina																											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 200 mg/kg

WEEKS ON STUDY	071	071	078	084	088	089	090	094	096	096	098	098	100	100	100	101	103	105	105	105	105	105	105	105	105
CARCASS ID	511	531	571	512	551	513	541	581	591	572	592	582	552	532	542	561	533	514	515	521	522	523	524	525	534
ALIMENTARY SYSTEM																									
Intestine large											+														
Intestine large, cecum											+														
Intestine large, colon											+														
Intestine large, rectum											+														
Intestine small											+		+												
Intestine small, duodenum											+														
Intestine small, ileum											+														
Leukemia mononuclear											X														
Intestine small, jejunum											+		+												
Schwannoma malignant													X												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X															
Leukemia mononuclear					X		X				X			X					X	X		X		X	X
Mesentery							+								+			+	+						
Leukemia mononuclear																									
Pancreas										+			+												
Fibrous histiocytoma										X															
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X																				
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X	X																					
Leukemia mononuclear					X						X														X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic											+		+												
Adenoma											X		X												
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X	X		X	X		X	X	X		X	X			X	X	X		X	X	X	X	X	X
Carcinoma															X										
Leukemia mononuclear														X											
Thyroid gland								+																	
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, carcinoma								X																	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary																									
Uterus	+											+		+	+										
Leukemia mononuclear														X											
Polyp stromal	X											X		X	X										
Vagina									+		+			+											+
Leukemia mononuclear											X														

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	535	543	544	545	553	554	555	562	563	564	565	573	574	575	583	584	585	593	594	595	601	602	603	604	605	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Intestine large																										1
Intestine large, cecum																										1
Intestine large, colon																										1
Intestine large, rectum																										1
Intestine small																										2
Intestine small, duodenum																										1
Intestine small, ileum																										1
Leukemia mononuclear																										1
Intestine small, jejunum																										2
Schwannoma malignant																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Leukemia mononuclear		X	X	X		X					X					X	X		X					X	X	19
Mesentery						+																				5
Leukemia mononuclear						X																				1
Pancreas																										2
Fibrous histiocytoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X										2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X																								1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Leukemia mononuclear						X																				4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X																				2
Pheochromocytoma benign							X																	X		2
Bilateral, pheochromocytoma benign																									X	1
Islets, pancreatic																										2
Adenoma																										2
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X							X	X	X		X	X		X	X	X	X		X	X		X		31
Carcinoma							X																			2
Leukemia mononuclear		X				X																				3
Thyroid gland						+									+									+		4
C-cell, adenoma															X											1
C-cell, carcinoma																								X		1
Follicular cell, carcinoma															X											2
GENERAL BODY SYSTEM																										
None											†															
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X				X																			3
Ovary			+									+	+													3
Uterus							+			+		+				+			+	+		+	+			12
Leukemia mononuclear																										1
Polyp stromal							X												X	X		X				8
Vagina																										4
Leukemia mononuclear																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	071	071	078	084	088	089	090	094	096	096	098	098	100	100	100	101	103	105	105	105	105	105	105	105	105	105
CARCASS ID	511	531	571	512	551	513	541	581	591	572	592	582	552	532	542	561	533	514	515	521	522	523	524	525	534
HEMATOPOIETIC SYSTEM																										
Blood																										
Bone marrow								+		+	+								+							
Fibrous histiocytoma										X																
Leukemia mononuclear											X															
Lymph node										+																
Mediastinal, fibrous histiocytoma										X																
Lymph node, mesenteric										+																
Fibrous histiocytoma										X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma										X																
Leukemia mononuclear					X		X				X			X					X	X		X		X	X
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X				X																
Fibroadenoma		X			X		X	X	X		X	X	X		X	X		X	X			X	X	X	X	
Leukemia mononuclear																										
Skin							+	+	+	+	+	+	+		+	+		+	+		+	+	+	+	+	
Subcutaneous tissue, fibroma																X			X							
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+																
Fibrous histiocytoma										X																
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland															X											
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant				X																						
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																										
Fibrous histiocytoma										X																
Leukemia mononuclear					X		X				X			X						X					X	
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X															
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X			X												X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 200 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	535	543	544	545	553	554	555	562	563	564	565	573	574	575	583	584	585	593	594	595	601	602	603	604	605	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																		+								1
Bone marrow																					+					5
Fibrous histiocytoma																										1
Leukemia mononuclear																										1
Lymph node																										1
Mediastinal, fibrous histiocytoma																										1
Lymph node, mesenteric																										1
Fibrous histiocytoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Leukemia mononuclear		X	X	X		X					X					X	X		X				X	X	X	20
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Fibroadenoma	X		X				X		X	X		X	X	X	X		X			X	X					28
Leukemia mononuclear		X																								1
Skin	+		+				-		+	+		+	+	+	+		+	+		+	+					29
Subcutaneous tissue, fibroma			X																							3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Fibrous histiocytoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																								X		1
Fibrous histiocytoma																										1
Leukemia mononuclear		X				X																				8
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X																				6

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 400 mg/kg

WEEKS ON STUDY	0220	0222	0233	0336	0340	0370	0375	0375	0380	0381	0382	0388	0390	0394	0395	0397	0399	1000	1000	1002	1005	1005	1015	1015
CARCASS ID	4611	4662	4551	4331	4332	4671	4691	4441	4421	4481	4211	4483	4482	4411	4222	4884	4233	4855	4241	5011	4633	4121	4133	4144	4155
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic														X											
Intestine small, ileum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X					X			X	X	X	X	X		
Lymphoma malignant lymphocytic														X											
Neoplastic nodule																	X								
Mesentery																	+	+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Lymphoma malignant lymphocytic														X											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X														
Lymphoma malignant lymphocytic														X											
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X														
Lymphoma malignant lymphocytic														X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Leukemia mononuclear															X				X	X	X	X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	
Leukemia mononuclear																		X							
Pheochromocytoma malignant														X											X
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X	X				X		X		
Carcinoma									X																
Leukemia mononuclear																						X			
Lymphoma malignant lymphocytic														X											
Pars intermedia, adenoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Lymphoma malignant lymphocytic														X											
C-cell, adenoma													X												
Follicular cell, adenoma																									
Follicular cell, carcinoma													X												
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Basosquamous tumor malignant																									
Carcinoma																							X		
Lymphoma malignant lymphocytic														X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Lymphoma malignant lymphocytic														X											
Polyp stromal															X							X	X	X	X
Vagina									M	M								+			+				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	42 25	43 33	43 34	43 35	44 43	44 44	44 45	45 52	45 53	45 54	45 55	46 64	46 65	47 72	47 73	47 74	47 75	49 92	49 93	49 94	49 95	50 02	50 03	50 04	50 05	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			46
Lymphoma malignant lymphocytic																										1
Intestine small, ileum	+	+	M	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			44
Intestine small, jejunum	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X			X	X	X			X		X			X	X		X					18
Lymphoma malignant lymphocytic																										1
Neoplastic nodule																										1
Mesentery							+						+							+	+					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X							1
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Papilloma squamous	X																					X				2
Stomach, glanduiar	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Lymphoma malignant lymphocytic																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								3
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													2
Leukemia mononuclear																										5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Pheochromocytoma malignant																										2
Pheochromocytoma benign							X	X								X										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X	X					X	X	X	X	X		X			X				X				X	15
Carcinoma																										1
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
C-cell, adenoma																				X				X		3
Follicular cell, adenoma			X																							1
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Adenoma																					X					1
Basosquamous tumor malignant																							X			1
Carcinoma																										1
Lymphoma malignant lymphocytic																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Lymphoma malignant lymphocytic																										1
Polyp stromal		X	X				X		X	X	X		X							X				X		14
Vagina																										2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	020	022	023	033	036	040	070	075	075	080	081	082	088	090	094	095	097	099	100	100	102	105	105	105	105
CARCASS ID	461	462	451	431	432	471	491	441	442	481	421	483	482	411	422	484	423	485	424	501	463	412	413	414	415
HEMATOPOIETIC SYSTEM																									
Blood																			+			+			
Leukemia mononuclear																			X			X			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Lymphoma malignant lymphocytic															X										
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, lymphoma malignant lymphocytic															X										
Mediastinal, leukemia mononuclear											X														
Mediastinal, lymphoma malignant lymphocytic															X										
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X												X	X	
Lymphoma malignant lymphocytic															X										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X															X		
Lymphoma malignant lymphocytic															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X					X			X		X	X	X	
Lymphoma malignant lymphocytic															X										
Sarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma							X					X	X			X		X		X			X	X	X
Leukemia mononuclear											X														
Lymphoma malignant lymphocytic															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
Papilloma														X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Leukemia mononuclear											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X					X			X		X	X	X		
Lymphoma malignant lymphocytic															X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
SPECIAL SENSES SYSTEM																									
Eye	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Lymphoma malignant lymphocytic															X										
Urethra												+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 400 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	425	433	434	435	443	444	445	452	453	454	455	464	465	472	473	474	475	492	493	494	495	502	503	504	505	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Leukemia mononuclear																										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, lymphoma malignant lymphocytic																										1
Mediastinal, leukemia mononuclear																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
Leukemia mononuclear																										4
Lymphoma malignant lymphocytic																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		3
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X			X		X			X		X			X	X		X					16
Lymphoma malignant lymphocytic																										1
Sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X												X													2
Fibroadenoma	X	X	X	X					X		X		X	X	X	X		X			X	X				22
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Papilloma					X																					2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Leukemia mononuclear																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Peripheral nerve	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X							X			X								10
Lymphoma malignant lymphocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant lymphocytic																										1
Urethra																										1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	5/49 (10%)	3/49 (6%)	3/47 (6%)
Adjusted Rates (b)	13.5%	9.1%	10.7%
Terminal Rates (c)	2/33 (6%)	3/33 (9%)	3/28 (11%)
Day of First Observation	695	730	730
Life Table Tests (d)	P=0.366N	P=0.369N	P=0.455N
Logistic Regression Tests (d)	P=0.382N	P=0.348N	P=0.474N
Cochran-Armitage Trend Test (d)	P=0.302N		
Fisher Exact Test (d)		P=0.357N	P=0.381N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	7/49 (14%)	3/49 (6%)	5/47 (11%)
Adjusted Rates (b)	18.0%	9.1%	16.7%
Terminal Rates (c)	3/33 (9%)	3/33 (9%)	4/28 (14%)
Day of First Observation	364	730	652
Life Table Tests (d)	P=0.409N	P=0.171N	P=0.499N
Logistic Regression Tests (d)	P=0.386N	P=0.164N	P=0.468N
Cochran-Armitage Trend Test (d)	P=0.332N		
Fisher Exact Test (d)		P=0.159N	P=0.410N
Clitoral Gland: Adenoma			
Overall Rates (a)	1/45 (2%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	3.6%	9.1%	3.7%
Terminal Rates (c)	1/28 (4%)	3/33 (9%)	1/27 (4%)
Day of First Observation	730	730	730
Life Table Tests (d)	P=0.602	P=0.365	P=0.754
Logistic Regression Tests (d)	P=0.602	P=0.365	P=0.754
Cochran-Armitage Trend Test (d)	P=0.588N		
Fisher Exact Test (d)		P=0.349	P=0.736N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/45 (4%)	3/50 (6%)	2/48 (4%)
Adjusted Rates (b)	6.1%	9.1%	7.4%
Terminal Rates (c)	1/28 (4%)	3/33 (9%)	2/27 (7%)
Day of First Observation	698	730	730
Life Table Tests (d)	P=0.571	P=0.552	P=0.666
Logistic Regression Tests (d)	P=0.560	P=0.562	P=0.664
Cochran-Armitage Trend Test (d)	P=0.567N		
Fisher Exact Test (d)		P=0.550	P=0.667N
Liver: Neoplastic Nodule			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	14.6%	0.0%	2.9%
Terminal Rates (c)	4/33 (12%)	0/33 (0%)	0/29 (0%)
Day of First Observation	715		676
Life Table Tests (d)	P=0.050N	P=0.035N	P=0.143N
Logistic Regression Tests (d)	P=0.048N	P=0.033N	P=0.140N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.028N	P=0.102N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	(f) 28/50 (56%)	28/50 (56%)	22/50 (44%)
Adjusted Rates (b)	71.4%	64.5%	62.1%
Terminal Rates (c)	22/33 (67%)	18/33 (55%)	16/29 (55%)
Day of First Observation	520	495	485
Life Table Tests (d)	P=0.356N	P=0.568N	P=0.378N
Logistic Regression Tests (d)	P=0.304N	P=0.552N	P=0.353N
Cochran-Armitage Trend Test (d)	P=0.135N		
Fisher Exact Test (d)		P=0.580N	P=0.159N

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

	Vehicle Control	200 mg/kg	400 mg/kg
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (e)	(f) 29/50 (58%)	30/50 (60%)	22/50 (44%)
Adjusted Rates (b)	72.2%	66.1%	62.1%
Terminal Rates (c)	22/33 (67%)	18/33 (55%)	16/29 (55%)
Day of First Observation	520	495	485
Life Table Tests (d)	P=0.307N	P=0.501	P=0.316N
Logistic Regression Tests (d)	P=0.235N	P=0.528	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.096N		
Fisher Exact Test (d)		P=0.500	P=0.115N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	23/49 (47%)	31/49 (63%)	15/49 (31%)
Adjusted Rates (b)	59.4%	71.4%	46.7%
Terminal Rates (c)	17/32 (53%)	20/32 (63%)	12/29 (41%)
Day of First Observation	463	495	676
Life Table Tests (d)	P=0.180N	P=0.115	P=0.164N
Logistic Regression Tests (d)	P=0.132N	P=0.081	P=0.146N
Cochran-Armitage Trend Test (d)	P=0.064N		
Fisher Exact Test (d)		P=0.077	P=0.073N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	3/49 (6%)	2/49 (4%)	1/49 (2%)
Adjusted Rates (b)	8.5%	5.7%	2.4%
Terminal Rates (c)	2/32 (6%)	1/32 (3%)	0/29 (0%)
Day of First Observation	674	697	554
Life Table Tests (d)	P=0.266N	P=0.507N	P=0.355N
Logistic Regression Tests (d)	P=0.229N	P=0.495N	P=0.308N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	26/49 (53%)	33/49 (67%)	16/49 (33%)
Adjusted Rates (b)	65.7%	74.5%	48.0%
Terminal Rates (c)	19/32 (59%)	21/32 (66%)	12/29 (41%)
Day of First Observation	463	495	554
Life Table Tests (d)	P=0.114N	P=0.155	P=0.101N
Logistic Regression Tests (d)	P=0.065N	P=0.115	P=0.074N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test (d)		P=0.108	P=0.033N
Subcutaneous Tissue: Fibroma			
Overall Rates (e)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	8.7%	0.0%
Terminal Rates (c)	0/33 (0%)	2/33 (6%)	0/29 (0%)
Day of First Observation		702	
Life Table Tests (d)	P=0.602	P=0.121	(g)
Logistic Regression Tests (d)	P=0.600	P=0.120	(g)
Cochran-Armitage Trend Test (d)	P=0.639N		
Fisher Exact Test (d)		P=0.121	(g)
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/50 (4%)	(h) 1/4 (25%)	3/50 (6%)
Adjusted Rates (b)	6.1%		9.4%
Terminal Rates (c)	2/33 (6%)		2/29 (7%)
Day of First Observation	730		629
Life Table Test (d)			P=0.442
Logistic Regression Test (d)			P=0.438
Fisher Exact Test (d)			P=0.500

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

	Vehicle Control	200 mg/kg	400 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	(h) 2/4 (50%)	3/50 (6%)
Adjusted Rates (b)	6.1%		9.4%
Terminal Rates (c)	2/33 (6%)		2/29 (7%)
Day of First Observation	730		629
Life Table Test (d)			P=0.442
Logistic Regression Test (d)			P=0.438
Fisher Exact Test (d)			P=0.500
Uterus: Stromal Polyp			
Overall Rates (e)	12/50 (24%)	8/50 (16%)	14/50 (28%)
Adjusted Rates (b)	29.6%	20.6%	46.4%
Terminal Rates (c)	7/33 (21%)	4/33 (12%)	13/29 (45%)
Day of First Observation	364	491	659
Life Table Tests (d)	P=0.241	P=0.241N	P=0.271
Logistic Regression Tests (d)	P=0.306	P=0.263N	P=0.322
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.212N	P=0.433
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	15/50 (30%)	20/50 (40%)	18/50 (36%)
Adjusted Rates (b)	37.3%	53.3%	50.9%
Terminal Rates (c)	9/33 (27%)	16/33 (48%)	12/29 (41%)
Day of First Observation	534	613	520
Life Table Tests (d)	P=0.163	P=0.217	P=0.194
Logistic Regression Tests (d)	P=0.163	P=0.211	P=0.205
Cochran-Armitage Trend Test (d)	P=0.301		
Fisher Exact Test (d)		P=0.201	P=0.335

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) A carcinoma was also observed in an animal bearing a fibroadenoma.
(g) No P value is reported because no tumors were observed in the 400 mg/kg and vehicle control groups.
(h) Incomplete sampling of tissues

TABLE B4. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	0/49
Allyl isovalerate	1/50
HC Red No. 3	0/50
C.I. Acid Orange 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
Allyl isothiocyanate	0/50
Geranyl acetate	1/50
TOTAL	(b) 3/449 (0.7%)
SD (c)	1.00%
Range (d)	
High	1/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 9/2,085 (0.4%)
SD (c)	0.95%
Range (d)	
High	(b) 2/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) All squamous cell papillomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papilloma, NOS, seven squamous cell papillomas, and one squamous cell carcinoma

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(1)	(50)
Parasite metazoan	1 (2%)		5 (10%)
Intestine large, colon	(49)	(1)	(50)
Parasite metazoan	3 (6%)		1 (2%)
Intestine large, rectum	(48)	(1)	(50)
Parasite metazoan	4 (8%)		5 (10%)
Intestine small, duodenum	(49)	(1)	(46)
Erosion			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	4 (8%)	
Basophilic focus	41 (82%)	43 (86%)	36 (72%)
Clear cell focus	2 (4%)	4 (8%)	3 (6%)
Developmental malformation	4 (8%)	10 (20%)	7 (14%)
Focal cellular change	3 (6%)		2 (4%)
Granuloma	13 (26%)	15 (30%)	21 (42%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic	4 (8%)	9 (18%)	3 (6%)
Mixed cell focus	1 (2%)	1 (2%)	
Bile duct, cyst multilocular	1 (2%)		
Bile duct, hyperplasia	25 (50%)	19 (38%)	12 (24%)
Centrilobular, atrophy	1 (2%)	5 (10%)	4 (8%)
Hepatocyte, hyperplasia, nodular	2 (4%)	5 (10%)	7 (14%)
Hepatocyte, vacuolization cytoplasmic	3 (6%)	4 (8%)	1 (2%)
Kupffer cell, hyperplasia		1 (2%)	
Kupffer cell, pigmentation	2 (4%)		3 (6%)
Lobules, necrosis	3 (6%)	6 (12%)	4 (8%)
Mesentery	(9)	(5)	(6)
Accessory spleen			1 (17%)
Infiltration cellular, histiocytic	1 (11%)		
Artery, hypertrophy			2 (33%)
Artery, inflammation, chronic active			2 (33%)
Fat, inflammation, chronic		1 (20%)	
Fat, inflammation, granulomatous	2 (22%)	2 (40%)	1 (17%)
Fat, inflammation, suppurative			1 (17%)
Fat, mineralization		3 (60%)	1 (17%)
Fat, necrosis	6 (67%)	5 (100%)	3 (50%)
Pancreas	(48)	(2)	(50)
Atrophy	4 (8%)	1 (50%)	2 (4%)
Ectopic tissue	1 (2%)		
Hyperplasia, nodular	5 (10%)		5 (10%)
Inflammation, chronic			2 (4%)
Salivary glands	(50)		(50)
Ectasia			1 (2%)
Inflammation, chronic	2 (4%)		
Stomach, forestomach	(50)	(50)	(50)
Edema	2 (4%)		1 (2%)
Fibrosis			1 (2%)
Inflammation, chronic	2 (4%)		2 (4%)
Inflammation, suppurative	1 (2%)		
Mineralization	1 (2%)		
Ulcer	1 (2%)	1 (2%)	1 (2%)
Mucosa, dysplasia		1 (2%)	
Mucosa, hyperplasia	5 (10%)	2 (4%)	3 (6%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(50)	(50)	(50)
Cyst		1 (2%)	
Edema	1 (2%)		
Erosion		1 (2%)	3 (6%)
Inflammation, granulomatous	1 (2%)		1 (2%)
Mineralization	5 (10%)	8 (16%)	1 (2%)
Ulcer	1 (2%)		1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Cardiomyopathy	20 (40%)	15 (30%)	19 (38%)
Thrombus			1 (2%)
Epicardium, inflammation, chronic active			1 (2%)
Myocardium, inflammation, chronic	7 (14%)	8 (16%)	1 (2%)
Myocardium, mineralization		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Accessory adrenal cortical nodule	8 (16%)	8 (16%)	3 (6%)
Angiectasis	5 (10%)	7 (14%)	8 (16%)
Basophilic focus		1 (2%)	1 (2%)
Clear cell focus	9 (18%)	10 (20%)	8 (16%)
Cyst multilocular		1 (2%)	
Hemorrhage			2 (4%)
Hyperplasia	6 (12%)	5 (10%)	5 (10%)
Necrosis			3 (6%)
Vacuolization cytoplasmic, diffuse	1 (2%)	3 (6%)	
Adrenal gland, medulla	(49)	(49)	(47)
Cyst	1 (2%)		
Fibrosis	1 (2%)		
Hyperplasia	1 (2%)	4 (8%)	1 (2%)
Inflammation, chronic		1 (2%)	
Islets, pancreatic	(48)	(2)	(50)
Hyperplasia			1 (2%)
Pituitary gland	(49)	(49)	(49)
Pars distalis, angiectasis	3 (6%)	4 (8%)	8 (16%)
Pars distalis, cyst	14 (29%)	15 (31%)	9 (18%)
Pars distalis, hyperplasia	4 (8%)	4 (8%)	10 (20%)
Pars distalis, pigmentation	1 (2%)	1 (2%)	2 (4%)
Pars intermedia, angiectasis		1 (2%)	
Pars intermedia, cyst		2 (4%)	1 (2%)
Pars intermedia, hyperplasia			1 (2%)
Pars nervosa, hyperplasia	1 (2%)		1 (2%)
Thyroid gland	(50)	(4)	(50)
Ultimobranchial cyst	1 (2%)		1 (2%)
C-cell, hyperplasia	7 (14%)	1 (25%)	7 (14%)
Follicle, cyst	1 (2%)	1 (25%)	
Follicular cell, hyperplasia	1 (2%)		1 (2%)
GENERAL BODY SYSTEM			
None			

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
GENITAL SYSTEM			
Clitoral gland	(45)	(50)	(48)
Ectasia	6 (13%)	2 (4%)	7 (15%)
Hyperplasia	3 (7%)	1 (2%)	7 (15%)
Inflammation, chronic	6 (13%)	6 (12%)	4 (8%)
Inflammation, suppurative	6 (13%)	2 (4%)	12 (25%)
Metaplasia, squamous			1 (2%)
Ovary	(49)	(3)	(50)
Atrophy	1 (2%)		
Cyst	4 (8%)	2 (67%)	7 (14%)
Hemorrhage	1 (2%)		
Inflammation, chronic	1 (2%)		
Uterus	(49)	(12)	(50)
Angiectasis			1 (2%)
Cyst		3 (25%)	1 (2%)
Hemorrhage		1 (8%)	2 (4%)
Hydrometra	2 (4%)	1 (8%)	1 (2%)
Hyperplasia, cystic	4 (8%)	1 (8%)	4 (8%)
Inflammation, suppurative	1 (2%)	1 (8%)	1 (2%)
Necrosis			1 (2%)
Endometrium, dysplasia			1 (2%)
HEMATOPOIETIC SYSTEM			
Blood	(2)	(1)	(2)
Anemia	1 (50%)	1 (100%)	2 (100%)
Leukocytosis	1 (50%)		
Bone marrow	(50)	(5)	(50)
Hyperplasia, reticulum cell	3 (6%)	1 (20%)	5 (10%)
Myelofibrosis	1 (2%)		
Proliferation	3 (6%)		
Lymph node	(50)	(1)	(50)
Mediastinal, hyperplasia, plasma cell			1 (2%)
Lymph node, mandibular	(46)		(47)
Hyperplasia, plasma cell	1 (2%)		2 (4%)
Lymphatic, dilatation	2 (4%)		1 (2%)
Lymph node, mesenteric	(48)	(1)	(50)
Depletion	1 (2%)		
Hemorrhage	1 (2%)		2 (4%)
Pigmentation			1 (2%)
Spleen	(50)	(50)	(50)
Congestion	1 (2%)	1 (2%)	
Fibrosis	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	6 (12%)	10 (20%)	4 (8%)
Hyperplasia, re cell	1 (2%)		1 (2%)
Necrosis		2 (4%)	
Pigmentation, hemosiderin	3 (6%)	7 (14%)	7 (14%)
Lymphoid follicle, atrophy			1 (2%)
Red pulp, atrophy	1 (2%)		1 (2%)
Thymus	(47)		(46)
Cyst	1 (2%)		1 (2%)
Fibrosis	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	43 (86%)	45 (90%)	32 (64%)
Hyperplasia, lobular	8 (16%)	10 (20%)	3 (6%)
Skin	(50)	(29)	(50)
Acanthosis	1 (2%)	1 (3%)	
Fibrosis	1 (2%)		
Inflammation, chronic		1 (3%)	
Inflammation, suppurative	1 (2%)		
Ulcer	1 (2%)		
Nipple, hypertrophy		1 (3%)	
Subcutaneous tissue, inflammation, granulomatous			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, hyperostosis	6 (12%)	7 (14%)	1 (2%)
Femur, hyperostosis	7 (14%)	7 (14%)	1 (2%)
Sternum, hyperostosis	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	7 (14%)	16 (32%)	3 (6%)
Hemorrhage			2 (4%)
Hydrocephalus	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic			2 (4%)
Vacuolization cytoplasmic			1 (2%)
Peripheral nerve	(47)	(50)	(49)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Spinal cord	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Axon, white matter, degeneration	1 (2%)		
Gray matter, degeneration	2 (4%)	1 (2%)	1 (2%)
Parenchyma, white matter, degeneration, multifocal		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Congestion	2 (4%)	2 (4%)	4 (8%)
Fibrosis	1 (2%)		
Infiltration cellular, histiocytic	26 (52%)	14 (28%)	14 (28%)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, suppurative			1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	2 (4%)
Mediastinum, inflammation, chronic active	1 (2%)		
Subpleura, inflammation, chronic active	1 (2%)		
Nose	(50)		(50)
Exudate	4 (8%)		6 (12%)
Fungus	1 (2%)		
Inflammation, chronic	2 (4%)		
Mucosa, hyperplasia			1 (2%)
Mucosa, metaplasia, squamous	2 (4%)		
Trachea	(50)		(50)
Exudate			1 (2%)
Inflammation, chronic			1 (2%)
Mucosa, metaplasia, squamous			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(49)
Cataract	21 (42%)	19 (38%)	25 (51%)
Hemorrhage		1 (2%)	
Cornea, inflammation, chronic			1 (2%)
Cornea, neovascularization			1 (2%)
Retina, atrophy	43 (86%)	42 (84%)	40 (82%)
Sclera, mineralization	5 (10%)	11 (22%)	6 (12%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Angiectasis		1 (2%)	
Cyst		2 (4%)	
Fibrosis			1 (2%)
Hemorrhage			1 (2%)
Hydronephrosis		2 (4%)	
Infarct	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	3 (6%)	7 (14%)	1 (2%)
Inflammation, suppurative		1 (2%)	3 (6%)
Mineralization	43 (86%)	45 (90%)	41 (82%)
Nephropathy	33 (66%)	41 (82%)	34 (68%)
Papilla, necrosis		1 (2%)	
Renal tubule, cytoplasmic alteration	1 (2%)		
Renal tubule, degeneration	2 (4%)	3 (6%)	
Renal tubule, dilatation			2 (4%)
Renal tubule, necrosis	1 (2%)		1 (2%)
Renal tubule, pigmentation			2 (4%)
Transitional epithelium, hyperplasia		2 (4%)	2 (4%)
Urethra			(1)
Calculus micro observation only			1 (100%)
Inflammation, suppurative			1 (100%)
Mucosa, hyperplasia			1 (100%)
Urinary bladder	(49)		(49)
Edema	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, suppurative			1 (2%)
Mineralization			1 (2%)
Ulcer			1 (2%)
Mucosa, hyperplasia			3 (6%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, jejunum	(50)	*(50)	(49)
Adenocarcinoma	1 (2%)	1 (2%)	1 (2%)
Polyp adenomatous			1 (2%)
Peyer's patch, lymphoma malignant mixed	1 (2%)		
Liver	(50)	*(50)	(50)
Fibrosarcoma, metastatic, spleen		1 (2%)	
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
Hepatocellular carcinoma	12 (24%)	6 (12%)	7 (14%)
Hepatocellular adenoma	8 (16%)	6 (12%)	13 (26%)
Hepatocellular adenoma, multiple			1 (2%)
Histiocytic sarcoma		1 (2%)	
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant mixed			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Fibrosarcoma, metastatic, spleen		1 (2%)	
Hemangiosarcoma	1 (2%)		
Pancreas	(50)	*(50)	(49)
Fibrosarcoma, metastatic, spleen		1 (2%)	
Stomach, forestomach	(50)	(49)	(50)
Papilloma squamous	1 (2%)	2 (4%)	5 (10%)
Stomach, glandular	(50)	(49)	(50)
Sarcoma	1 (2%)		
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(50)
Spindle cell, adenoma			2 (4%)
Adrenal gland, medulla	(49)	*(50)	(50)
Pheochromocytoma benign	2 (4%)		2 (4%)
Islets, pancreatic	(50)	*(50)	(49)
Adenoma	1 (2%)		1 (2%)
Pituitary gland	(44)	*(50)	(47)
Pars distalis, adenoma	1 (2%)		1 (2%)
Thyroid gland	(49)	*(50)	(49)
Follicular cell, adenoma	2 (4%)		1 (2%)
Follicular cell, carcinoma			2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Prostate	(49)	*(50)	(50)
Lymphoma malignant mixed	1 (2%)		
Testes	(50)	*(50)	(50)
Interstitial cell, adenoma			1 (2%)

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

	Vehicle Control	200 mg/kg	400 mg/kg
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	*(50)	(50)
Iliac, lymphoma malignant mixed			2 (4%)
Inguinal, lymphoma malignant histiocytic			1 (2%)
Mediastinal, lymphoma malignant histiocytic			1 (2%)
Mediastinal, lymphoma malignant mixed			1 (2%)
Pancreatic, lymphoma malignant histiocytic			1 (2%)
Renal, lymphoma malignant histiocytic			1 (2%)
Renal, lymphoma malignant mixed			1 (2%)
Lymph node, mandibular	(46)	*(50)	(47)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant mixed			3 (6%)
Lymph node, mesenteric	(46)	*(50)	(48)
Fibrosarcoma, metastatic, spleen		1 (2%)	
Histiocytic sarcoma		1 (2%)	
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)		2 (4%)
Spleen	(50)	*(50)	(50)
Fibrosarcoma		1 (2%)	
Hemangiosarcoma		1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, mesentery	1 (2%)		
Lymphoma malignant histiocytic			2 (4%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)		3 (6%)
Thymus	(41)	*(50)	(45)
Lymphoma malignant mixed	1 (2%)		
INTEGUMENTARY SYSTEM			
Skin	(50)	*(50)	(50)
Papilloma squamous	1 (2%)		
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)	3 (6%)
Subcutaneous tissue, fibrosarcoma	3 (6%)	3 (6%)	4 (8%)
Subcutaneous tissue, sarcoma			1 (2%)
Subcutaneous tissue, sarcoma, multiple		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Hemangiosarcoma, metastatic, mesentery	1 (2%)		
NERVOUS SYSTEM			
None			
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	5 (10%)
Carcinoma, metastatic, harderian gland	1 (2%)		
Fibrosarcoma, metastatic, skin			2 (4%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		1 (2%)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant mixed	1 (2%)		1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Mediastinum, fibrosarcoma, metastatic, spleen		1 (2%)	

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

	Vehicle Control	200 mg/kg	400 mg/kg
RESPIRATORY SYSTEM (Continued)			
Nose	(50)	*(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)		
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	2 (4%)	2 (4%)	2 (4%)
Carcinoma	1 (2%)		
URINARY SYSTEM			
Urinary bladder	(50)	*(50)	(50)
Papilloma			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant mixed	1 (2%)		3 (6%)
Hemangioma	1 (2%)		
Hemangiosarcoma	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic		2 (4%)	
Lymphoma malignant histiocytic			2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	5	4	3
Moribund	9	11	13
Terminal sacrifice	32	33	31
Gavage death	3	2	1
Dosing accident	1		1
Natural death			1
TUMOR SUMMARY			
Total animals with primary neoplasms **	36	26	40
Total primary neoplasms	50	32	62
Total animals with benign neoplasms	21	13	28
Total benign neoplasms	27	13	35
Total animals with malignant neoplasms	20	17	25
Total malignant neoplasms	23	19	27
Total animals with secondary neoplasms ***	4	1	3
Total secondary neoplasms	8	5	3

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

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

WEEKS ON STUDY	0 0 1	0 0 1	0 0 2	0 0 2	0 6 4	0 6 5	0 8 0	0 8 3	0 8 3	0 8 7	0 9 2	0 9 5	0 9 5	0 9 7	1 0 0	1 0 2	1 0 3	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6
CARCASS ID	1 0 1 1	0 5 1 1	0 6 1 1	0 7 1 1	0 3 1 1	0 2 1 1	0 8 1 1	0 5 2 1	0 9 1 1	0 7 3 1	0 1 1 2	0 8 2 1	0 8 3 1	0 4 1 2	0 1 2 2	0 3 2 2	0 6 2 2	0 9 2 1	0 1 3 1	0 1 4 1	0 1 5 2	0 2 2 2	0 2 3 2	0 2 4 2	0 2 5 2
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Peyer's patch, lymphoma malignant mixed														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Hepatocellular carcinoma					X			X	X	X		X	X					X	X						
Hepatocellular adenoma								X							X	X									
Mesentery							+		+													+		+	
Hemangiosarcoma							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma					X																				
Tooth							+								+								+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign								X		X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma						X																			
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma						X																			X
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																		+							
Prostate	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											
Seminal vesicle																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Blood					+																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, mesentery							X																		
Lymphoma malignant mixed														X											
Thymus	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Lymphoma malignant mixed														X											

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

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

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	033	034	035	042	043	044	045	053	054	055	063	064	065	072	074	075	084	085	093	094	095	102	103	104	105	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma							X																			1
Peyer's patch, lymphoma malignant mixed																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatocellular carcinoma															X			X			X	X				12
Hepatocellular adenoma					X	X			X							X									X	8
Mesentery																+										5
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Tooth			+			+	+	+	+		+	+	+	+		+	+	+	+	+					+	20
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland			+																							2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										1
Seminal vesicle																	+		+							2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Lymphoma malignant mixed																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, meta., mesentery																										1
Lymphoma malignant mixed																										1
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	M	+	+	+	+	M	+	+	+	41
Lymphoma malignant mixed																										1

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

WEEKS ON STUDY	001	001	002	002	064	065	080	083	083	087	092	095	095	097	100	102	103	105	106	106	106	106	106	106	106
CARCASS ID	101	051	061	071	031	021	081	052	091	073	011	082	083	041	012	032	062	092	013	014	015	022	023	024	025
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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma										X	X												X		
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+											+							
Alveolar/bronchiolar carcinoma, metastatic, lung																		X							
Hemangiosarcoma, metastatic, mesentery							X																		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X											X				X				
Alveolar/bronchiolar carcinoma																		X			X				
Carcinoma, metastatic, harderian gland																	X								
Hepatocellular carcinoma, metastatic, liver								X										X							
Lymphoma malignant mixed														X											
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear									+																
Harderian gland									+								+								
Adenoma									X																
Carcinoma																	X								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	033	034	035	042	043	044	045	053	054	055	063	064	065	072	074	075	084	085	093	094	095	102	103	104	105	TOTAL: TISSUES TUMORS
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	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous													X													1
Subcutaneous tissue, fibroma										X						X										2
Subcutaneous tissue, fibrosarcoma																										3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma, meta., mesentery																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X								X														6
Alveolar/bronchiolar carcinoma								X																		3
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										2
Lymphoma malignant mixed																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Harderian gland																								+		3
Adenoma																								X		2
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 200 mg/kg

WEEKS ON STUDY	001	001	032	045	072	072	076	078	082	083	083	090	100	100	100	103	104	106	106	106	106	106	106	106	106
CARCASS ID	221	261	271	241	292	293	262	242	232	272	301	291	222	281	294	223	251	211	212	213	214	215	224	225	233
ALIMENTARY SYSTEM																									
Esophagus	+	+																							
Intestine small													+												
Intestine small, duodenum													M												
Intestine small, ileum													+												
Intestine small, jejunum													+												
Adenocarcinoma																									
Liver							+	+	+	+			+				+	+			+		+		+
Fibrosarcoma, metastatic, spleen													X												
Hepatocellular carcinoma							X		X	X											X				
Hepatocellular adenoma													X					X					X		X
Histiocytic sarcoma																	X								
Mesentery													+												
Fibrosarcoma, metastatic, spleen													X												
Pancreas													+												
Fibrosarcoma, metastatic, spleen													X												
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous								X																	
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																+									
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart			+																						
ENDOCRINE SYSTEM																									
None																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Coagulating gland																									
Penis						+																			
Preputial gland				+						+					+					+				
Seminal vesicle																									
HEMATOPOIETIC SYSTEM																									
Blood																									
Lymph node													+		+		+								
Lymph node, mesenteric													+		+		+								
Fibrosarcoma, metastatic, spleen													X												
Histiocytic sarcoma																	X								
Lymphoma malignant lymphocytic																									
Spleen													+	+	+	+	+								
Fibrosarcoma													X												
Hemangiosarcoma																	X								
Lymphoma malignant lymphocytic																X									
INTEGUMENTARY SYSTEM																									
Skin			+	+		+			+	+	+	+	+		+			+	+	+	+	+	+	+	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																				X					
Subcutaneous tissue, sarcoma, multiple															X										
MUSCULOSKELETAL SYSTEM																									
Skeletal muscle	+																								
NERVOUS SYSTEM																									
None																									
RESPIRATORY SYSTEM																									
Lung	+		+							+		+	+	+		+				+				
Alveolar/bronchiolar adenoma																+									
Alveolar/bronchiolar carcinoma														+											
Mediastinum, fibrosarcoma, metastatic, spleen													X												
Trachea	+																								
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney									+																
Urinary bladder						+												+							

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 200 mg/kg (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	234	235	254	231	243	244	245	252	253	255	263	264	265	273	274	275	282	283	284	285	295	302	303	304	305		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											2
Intestine small																						+					2
Intestine small, duodenum																											
Intestine small, ileum																											1
Intestine small, jejunum																						+					2
Adenocarcinoma																						X					1
Liver			+	+		+	+				+					+	+			+							18
Fibrosarcoma, metastatic, spleen																											1
Hepatocellular carcinoma							X				X																6
Hepatocellular adenoma			X														X										6
Histiocytic sarcoma																											1
Mesentery									+		+	+							+								5
Fibrosarcoma, metastatic, spleen																											1
Pancreas																			+								2
Fibrosarcoma, metastatic, spleen																											1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Papilloma squamous												X															2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Tongue																											1
Tooth																+											1
CARDIOVASCULAR SYSTEM																											
Heart																											1
ENDOCRINE SYSTEM																											
None																											
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Coagulating gland																			+								1
Penis																											1
Preputial gland			M																			+					5
Seminal vesicle	+	+												+				+					+				5
HEMATOPOIETIC SYSTEM																											
Blood				+																		+					2
Lymph node					+									+													5
Lymph node, mesenteric					+									+													5
Fibrosarcoma, metastatic, spleen																											1
Histiocytic sarcoma																											1
Lymphoma malignant lymphocytic														X													1
Spleen		+					+																				7
Fibrosarcoma																											1
Hemangiosarcoma																											1
Lymphoma malignant lymphocytic																											1
INTEGUMENTARY SYSTEM																											
Skin		+		+					+					+	+	+	+				+	+		+			26
Subcutaneous tissue, fibroma															X												1
Subcutaneous tissue, fibrosarcoma				X													X										3
Subcutaneous tissue, sarcoma, multiple																											1
MUSCULOSKELETAL SYSTEM																											
Skeletal muscle																											1
NERVOUS SYSTEM																											
None																											
RESPIRATORY SYSTEM																											
Lung	+		+				+						+		+								+				14
Alveolar/bronchiolar adenoma							X																				2
Alveolar/bronchiolar carcinoma																							X				2
Mediastinum, fibrosarcoma, metastatic, spleen																											1
Trachea																											1
SPECIAL SENSES SYSTEM																											
Eye													+						+								2
Harderian gland													+						+								2
Adenoma													X						X								2
URINARY SYSTEM																											
Kidney				+																							2
Urinary bladder																											2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 400 mg/kg

WEEKS ON STUDY	0 0 2	0 4 2	0 5 0	0 6 8	0 6 9	0 7 6	0 7 7	0 8 2	0 8 2	0 8 2	0 8 3	0 8 3	0 9 2	0 9 4	0 9 5	0 9 8	0 9 9	1 0 3	1 0 3	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6
CARCASS ID	1 2 1	1 6 1	1 5 1	1 5 2	1 9 1	1 7 1	1 8 2	1 1 1	1 9 2	1 7 2	1 6 3	2 0 1	1 3 1	1 7 3	1 2 2	1 1 2	1 9 3	2 0 2	1 5 3	1 1 3	1 1 4	1 1 5	1 2 3	1 2 4	1 2 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma				X				X	X	X	X														
Hepatocellular adenoma		X							X			X								X	X		X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant histiocytic																			X						
Lymphoma malignant mixed																								X	
Mesentery				+																					
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																			+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spindle cell, adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
Follicular cell, carcinoma																							X		
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+						+						+					+			+			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle																		+				+	+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																		X							

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 400 mg/kg (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	132	133	134	135	141	142	143	144	145	154	155	162	164	165	174	175	181	183	184	185	194	195	203	204	205		TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, ileum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenocarcinoma						X																					1
Polyp adenomatous																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma					X																						1
Hepatocellular carcinoma																X								X			7
Hepatocellular adenoma	X				X			X	X	X								X		X							13
Hepatocellular adenoma, multiple		X																									1
Lymphoma malignant histiocytic																			X								2
Lymphoma malignant mixed																											1
Mesentery																+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Papilloma squamous	X	X					X	X																	X		5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Tooth			+				+		+			+		+		+									+		14
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spindle cell, adenoma						X								X													2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma benign													X											X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Pars distalis, adenoma									X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Follicular cell, adenoma																						X					1
Follicular cell, carcinoma												X															2
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland						+	+																				7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle												+													+		5
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																											1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 400 mg/kg (Continued)

WEEKS ON STUDY	002	042	050	068	069	076	077	082	082	082	083	083	092	094	095	098	099	103	103	106	106	106	106	106	106
CARCASS ID	121	161	151	152	191	171	182	111	192	172	163	201	131	173	122	112	193	202	153	113	114	115	123	124	125
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, lymphoma malignant mixed																		X							
Inguinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant histiocytic																									
Mediastinal, lymphoma malignant mixed																		X							
Pancreatic, lymphoma malignant histiocytic																									
Renal, lymphoma malignant histiocytic																			X						
Renal, lymphoma malignant mixed																		X							
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed																		X						X	
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																			X						
Lymphoma malignant mixed																		X							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Lymphoma malignant histiocytic																			X						
Lymphoma malignant mixed																		X						X	
Thymus	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma						X								X											
Subcutaneous tissue, fibrosarcoma						X	X										X								
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+	+																						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma													X	X											
Fibrosarcoma, metastatic, skin						X	X																		
Hepatocellular carcinoma, metastatic, liver				X																					
Lymphoma malignant histiocytic																			X						
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear			+											+											
Harderian gland																		+							
Adenoma																		X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																				X					

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 400 mg/kg (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL:
CARCASS ID	132	133	134	135	141	142	143	144	145	154	155	162	164	165	174	175	181	183	184	185	194	195	203	204	205	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood										+						+										2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, lymphoma malignant mixed								X																		2
Inguinal, lymphoma malignant histiocytic																		X								1
Mediastinal, lymphoma malignant histiocytic																		X								1
Mediastinal, lymphoma malig. mixed																										1
Pancreatic, lymphoma malignant histiocytic																		X								1
Renal, lymphoma malignant histiocytic																										1
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																		X								1
Lymphoma malignant mixed								X																		3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Lymphoma malignant histiocytic																		X								2
Lymphoma malignant mixed								X																		2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymphoma malignant histiocytic																		X								2
Lymphoma malignant mixed								X																		3
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	+	+	M	M	+	M	+	M	M	+	12
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma															X											3
Subcutaneous tissue, fibrosarcoma																X										4
Subcutaneous tissue, sarcoma										X																1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																		X		X			X			5
Fibrosarcoma, metastatic, skin																										2
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										2
Harderian gland																	+									2
Adenoma																	X									2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																										1

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	8.2%	6.1%	6.2%
Terminal Rates (c)	1/32 (3%)	2/33 (6%)	1/31 (3%)
Day of First Observation	576	736	717
Life Table Tests (d)	P=0.422N	P=0.493N	P=0.517N
Logistic Regression Tests (d)	P=0.408N	P=0.497N	P=0.498N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Liver: Hepatocellular Adenoma			
Overall Rates (e)	8/50 (16%)	(f) 6/18 (33%)	14/50 (28%)
Adjusted Rates (b)	22.2%		39.9%
Terminal Rates (c)	5/32 (16%)		11/31 (35%)
Day of First Observation	576		293
Life Table Test (d)			P=0.102
Logistic Regression Test (d)			P=0.116
Fisher Exact Test (d)			P=0.114
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	12/50 (24%)	(f) 6/18 (33%)	7/50 (14%)
Adjusted Rates (b)	29.4%		17.0%
Terminal Rates (c)	5/32 (16%)		2/31 (6%)
Day of First Observation	448		471
Life Table Test (d)			P=0.199N
Logistic Regression Test (d)			P=0.158N
Fisher Exact Test (d)			P=0.154N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	19/50 (38%)	(f) 12/18 (67%)	20/50 (40%)
Adjusted Rates (b)	45.6%		50.8%
Terminal Rates (c)	10/32 (31%)		13/31 (42%)
Day of First Observation	448		293
Life Table Test (d)			P=0.448
Logistic Regression Test (d)			P=0.514
Fisher Exact Test (d)			P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	6/50 (12%)	(f) 2/14 (14%)	1/50 (2%)
Adjusted Rates (b)	17.0%		3.2%
Terminal Rates (c)	4/32 (13%)		1/31 (3%)
Day of First Observation	451		736
Life Table Test (d)			P=0.064N
Logistic Regression Test (d)			P=0.057N
Fisher Exact Test (d)			P=0.056N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	3/50 (6%)	(f) 2/14 (14%)	5/50 (10%)
Adjusted Rates (b)	9.1%		14.4%
Terminal Rates (c)	2/32 (6%)		3/31 (10%)
Day of First Observation	734		640
Life Table Test (d)			P=0.339
Logistic Regression Test (d)			P=0.346
Fisher Exact Test (d)			P=0.357

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

	Vehicle Control	200 mg/kg	400 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	8/50 (16%)	(f) 4/14 (29%)	6/50 (12%)
Adjusted Rates (b)	22.4%		17.5%
Terminal Rates (c)	5/32 (16%)		4/31 (13%)
Day of First Observation	451		640
Life Table Test (d)			P=0.412N
Logistic Regression Test (d)			P=0.385N
Fisher Exact Test (d)			P=0.387N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	6.3%	3.0%	7.9%
Terminal Rates (c)	2/32 (6%)	1/33 (3%)	1/31 (3%)
Day of First Observation	736	736	529
Life Table Tests (d)	P=0.390	P=0.489N	P=0.489
Logistic Regression Tests (d)	P=0.403	P=0.489N	P=0.504
Cochran-Armitage Trend Test (d)	P=0.400		
Fisher Exact Test (d)		P=0.500N	P=0.500
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	7.9%	9.1%	10.2%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	1/31 (3%)
Day of First Observation	609	736	529
Life Table Tests (d)	P=0.406	P=0.659N	P=0.483
Logistic Regression Tests (d)	P=0.424	P=0.660N	P=0.495
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661N	P=0.500
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	13.8%	12.1%	15.6%
Terminal Rates (c)	3/32 (9%)	4/33 (12%)	2/31 (6%)
Day of First Observation	609	736	529
Life Table Tests (d)	P=0.415	P=0.492N	P=0.477
Logistic Regression Tests (d)	P=0.440	P=0.497N	P=0.504
Cochran-Armitage Trend Test (d)	P=0.434		
Fisher Exact Test (d)		P=0.500N	P=0.500
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	7.9%	11.6%	13.2%
Terminal Rates (c)	1/32 (3%)	3/33 (9%)	2/31 (6%)
Day of First Observation	609	700	529
Life Table Tests (d)	P=0.278	P=0.504	P=0.344
Logistic Regression Tests (d)	P=0.294	P=0.504	P=0.355
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.500	P=0.357
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	7/50 (14%)
Adjusted Rates (b)	13.8%	14.6%	18.5%
Terminal Rates (c)	3/32 (9%)	4/33 (12%)	3/31 (10%)
Day of First Observation	609	700	529
Life Table Tests (d)	P=0.302	P=0.619N	P=0.362
Logistic Regression Tests (d)	P=0.323	P=0.628N	P=0.384
Cochran-Armitage Trend Test (d)	P=0.318		
Fisher Exact Test (d)		P=0.630N	P=0.380

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

	Vehicle Control	200 mg/kg	400 mg/kg
Forestomach: Squamous Papilloma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	3.1%	5.3%	16.1%
Terminal Rates (c)	1/32 (3%)	1/33 (3%)	5/31 (16%)
Day of First Observation	736	541	736
Life Table Tests (d)	P=0.054	P=0.504	P=0.094
Logistic Regression Tests (d)	P=0.057	P=0.502	P=0.094
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.102
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (e)	2/49 (4%)	(g) 0/0	3/49 (6%)
Adjusted Rates (b)	5.3%		9.7%
Terminal Rates (c)	1/32 (3%)		3/31 (10%)
Day of First Observation	451		736
Life Table Test (d)			P=0.492
Logistic Regression Test (d)			P=0.503
Fisher Exact Test (d)			P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	2.7%	5.8%	15.2%
Terminal Rates (c)	0/32 (0%)	1/33 (3%)	3/31 (10%)
Day of First Observation	675	717	717
Life Table Tests (d)	P=0.058	P=0.513	P=0.102
Logistic Regression Tests (d)	P=0.054	P=0.502	P=0.095
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.102

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) Incomplete sampling of tissues
(g) No thyroid gland tissue from the 200 mg/kg group was examined microscopically.

TABLE C4. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	0/48
Benzyl acetate	(b) 4/49
Allyl isovalerate	0/50
HC Red No. 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/50
Allyl isothiocyanate	0/49
Geranyl acetate	0/50
C.I. Acid Orange 3	(b) 4/49
Chlorinated paraffins (C_{12}, 60% chlorine)	0/50
TOTAL	8/445 (1.8%)
SD (c)	3.60%
Range (d)	
High	4/49
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 39/2,033 (1.9%)
SD (c)	2.76%
Range (d)	
High	(f) 4/46
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one squamous cell carcinoma and three squamous cell papillomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes two papillomas, NOS, and nine squamous cell carcinomas; all other tumors were squamous cell papillomas.
(f) All squamous cell papillomas; no more than one squamous cell carcinoma has been observed in any vehicle control group.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	200 mg/kg	400 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(2)	(50)
Inflammation, chronic	1 (2%)		
Muscularis, degeneration	1 (2%)		
Gallbladder	(45)		(46)
Epithelium, hyperplasia, focal			1 (2%)
Intestine small, jejunum	(50)	(2)	(49)
Diverticulum	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
Epithelium, hyperplasia, focal	1 (2%)		
Liver	(50)	(18)	(50)
Angiectasis, focal			1 (2%)
Cyst	2 (4%)		
Focal cellular change	1 (2%)		1 (2%)
Hematopoietic cell proliferation, multifocal			1 (2%)
Hemorrhage, focal			1 (2%)
Hepatodiaphragmatic nodule		1 (6%)	
Hyperplasia, lymphoid, focal		1 (6%)	
Necrosis, focal	1 (2%)		2 (4%)
Necrosis, multifocal	1 (2%)		2 (4%)
Vacuolization cytoplasmic, diffuse		1 (6%)	
Vacuolization cytoplasmic, focal		3 (17%)	
Mesentery	(5)	(5)	(2)
Hemorrhage, focal			1 (50%)
Fat, necrosis, focal	4 (80%)	3 (60%)	1 (50%)
Fat, necrosis, multifocal		1 (20%)	
Pancreas	(50)	(2)	(49)
Atrophy, focal	2 (4%)		1 (2%)
Cyst	2 (4%)		
Stomach, forestomach	(50)	(49)	(50)
Cyst		2 (4%)	4 (8%)
Hyperplasia, focal	7 (14%)	6 (12%)	15 (30%)
Hyperplasia, multifocal		2 (4%)	1 (2%)
Infiltration cellular, mast cell			1 (2%)
Inflammation, chronic, focal		1 (2%)	
Inflammation, suppurative, acute, focal	3 (6%)	5 (10%)	7 (14%)
Ulcer	1 (2%)		4 (8%)
Stomach, glandular	(50)	(49)	(50)
Inflammation, suppurative, acute, focal		1 (2%)	
Tongue		(1)	
Ectopic tissue		1 (100%)	
Tooth	(20)	(1)	(14)
Dysplasia	20 (100%)	1 (100%)	14 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(1)	(50)
Artery, inflammation, subacute			1 (2%)
Valve, inflammation, subacute			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)		(50)
Hemorrhage			1 (2%)
Hyperplasia, focal	2 (4%)		3 (6%)
Necrosis			1 (2%)
Spindle cell, hyperplasia			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
ENDOCRINE SYSTEM (Continued)			
Adrenal gland, medulla	(49)		(50)
Hemorrhage			1 (2%)
Hyperplasia, focal			2 (4%)
Necrosis			1 (2%)
Pituitary gland	(44)		(47)
Pars distalis, cyst			1 (2%)
Thyroid gland	(49)		(49)
Follicle, cyst	1 (2%)		
Follicle, degeneration, cystic	3 (6%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Coagulating gland		(1)	
Dilatation		1 (100%)	
Epididymis	(50)		(50)
Inflammation, chronic, focal			1 (2%)
Penis		(1)	
Hemorrhage		1 (100%)	
Inflammation, suppurative, acute		1 (100%)	
Necrosis		1 (100%)	
Preputial gland	(2)	(5)	(7)
Inflammation, suppurative, acute		2 (40%)	4 (57%)
Duct, cyst	2 (100%)	4 (80%)	4 (57%)
Seminal vesicle	(2)	(5)	(5)
Dilatation	2 (100%)	5 (100%)	3 (60%)
Inflammation, chronic			1 (20%)
Testes	(50)		(50)
Atrophy			4 (8%)
HEMATOPOIETIC SYSTEM			
Blood	(1)	(2)	(2)
Leukocytosis		1 (50%)	
Polychromasia		1 (50%)	2 (100%)
Bone marrow	(50)		(50)
Myeloid cell, hyperplasia			1 (2%)
Lymph node, mesenteric	(46)	(5)	(48)
Angiectasis	6 (13%)	2 (40%)	6 (13%)
Hemorrhage			1 (2%)
Hyperplasia	1 (2%)	1 (20%)	
Spleen	(50)	(7)	(50)
Atrophy	1 (2%)	1 (14%)	2 (4%)
Congestion		1 (14%)	
Developmental malformation			1 (2%)
Hematopoietic cell proliferation	9 (18%)	2 (29%)	10 (20%)
Hyperplasia, lymphoid	1 (2%)		
Thymus	(41)		(45)
Cyst	2 (5%)		
Hyperplasia			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
INTEGUMENTARY SYSTEM			
Skin	(50)	(26)	(50)
Abscess			1 (2%)
Alopecia			1 (2%)
Cyst epithelial inclusion		1 (4%)	
Developmental malformation			2 (4%)
Edema, focal	1 (2%)		
Fibrosis, focal	2 (4%)	2 (8%)	7 (14%)
Fibrosis, multifocal			1 (2%)
Foreign body, focal	1 (2%)		
Inflammation, subacute, focal	1 (2%)		2 (4%)
Inflammation, suppurative, acute, focal		1 (4%)	
Mineralization, focal	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(2)	(1)	(2)
Hemorrhage		1 (100%)	
Artery, inflammation, subacute			1 (50%)
NERVOUS SYSTEM			
Brain	(50)		(50)
Compression	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(14)	(50)
Congestion	2 (4%)		
Foreign body		1 (7%)	1 (2%)
Hemorrhage, focal		1 (7%)	
Hemorrhage, multifocal		1 (7%)	
Infiltration cellular, histiocytic	1 (2%)	2 (14%)	3 (6%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	3 (21%)	4 (8%)
Fat, mediastinum, necrosis, focal	1 (2%)		
Mediastinum, foreign body	4 (8%)		1 (2%)
Mediastinum, hemorrhage	1 (2%)		
Mediastinum, inflammation, suppurative, acute	1 (2%)		1 (2%)
Nose	(50)		(50)
Foreign body	10 (20%)		13 (26%)
Fungus	1 (2%)		
Inflammation, suppurative, acute	11 (22%)		14 (28%)
Nasolacrimal duct, inflammation, suppurative, acute	3 (6%)		
Trachea	(50)	(1)	(50)
Perforation		1 (100%)	
SPECIAL SENSES SYSTEM			
Eye		(2)	
Cornea, fibrosis		1 (50%)	
Cornea, inflammation, chronic		1 (50%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
URINARY SYSTEM			
Kidney	(50)	(2)	(50)
Fibrosis, focal			1 (2%)
Inflammation, chronic, focal	1 (2%)		
Metaplasia, osseous, focal	1 (2%)		3 (6%)
Mineralization, multifocal			1 (2%)
Cortex, cyst			3 (6%)
Glomerulus, amyloid deposition	1 (2%)		
Papilla, necrosis			1 (2%)
Renal tubule, degeneration, multifocal	3 (6%)		4 (8%)
Renal tubule, dilatation, multifocal		1 (50%)	2 (4%)
Renal tubule, necrosis, multifocal		1 (50%)	1 (2%)
Renal tubule, regeneration, multifocal		1 (50%)	1 (2%)
Urinary bladder	(50)	(2)	(50)
Hemorrhage, focal		1 (50%)	
Inflammation, subacute		1 (50%)	

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	300 mg/kg	600 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, rectum	(45)	*(50)	(49)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Intestine small, jejunum	(48)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Polyp adenomatous		1 (2%)	
Liver	(50)	*(50)	(49)
Hepatocellular carcinoma	1 (2%)	2 (4%)	1 (2%)
Hepatocellular adenoma	1 (2%)	1 (2%)	4 (8%)
Hepatocellular adenoma, multiple		1 (2%)	
Histiocytic sarcoma	2 (4%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)		2 (4%)
Lymphoma malignant mixed	4 (8%)	2 (4%)	5 (10%)
Mesentery	*(50)	*(50)	*(50)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)		
Lymphoma malignant mixed		1 (2%)	3 (6%)
Pancreas	(48)	*(50)	(48)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)		2 (4%)
Salivary glands	(49)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed			1 (2%)
Stomach, forestomach	(50)	(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	1 (2%)
Papilloma squamous		5 (10%)	6 (12%)
Squamous cell carcinoma			(a) 1 (2%)
Stomach, glandular	(50)	(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)		1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(50)
Adenoma	1 (2%)		
Adrenal gland, medulla	(50)	*(50)	(50)
Pheochromocytoma benign	1 (2%)		
Pituitary gland	(47)	*(50)	(48)
Pars distalis, adenoma	5 (11%)	1 (2%)	2 (4%)
Thyroid gland	(49)	*(50)	(49)
Lymphoma malignant lymphocytic	1 (2%)		
Follicular cell, adenoma	1 (2%)		1 (2%)
GENERAL BODY SYSTEM			
None			

(a) Diagnosis not confirmed by PWG or NTP pathologists. See Results p. 42.

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

	Vehicle Control	300 mg/kg	600 mg/kg
GENITAL SYSTEM			
Ovary	(47)	*(50)	(44)
Adenoma	1 (2%)		
Uterus	(50)	*(50)	(50)
Adenocarcinoma	1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)		
Leiomyoma		1 (2%)	
Lymphoma malignant lymphocytic	2 (4%)		1 (2%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed		1 (2%)	1 (2%)
Polyp stromal	1 (2%)		1 (2%)
Sarcoma stromal		2 (4%)	
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		1 (2%)
Lymphoma malignant mixed			1 (2%)
Bone marrow	(50)	*(50)	(50)
Hemangiosarcoma	1 (2%)		
Lymph node	(50)	*(50)	(50)
Axillary, adenocarcinoma, metastatic, mammary gland	1 (2%)		
Axillary, lymphoma malignant mixed		3 (6%)	1 (2%)
Bronchial, lymphoma malignant mixed		1 (2%)	
Iliac, histiocytic sarcoma	1 (2%)		
Iliac, lymphoma malignant lymphocytic	1 (2%)		
Iliac, lymphoma malignant			1 (2%)
Iliac, lymphoma malignant mixed		3 (6%)	1 (2%)
Inguinal, lymphoma malignant mixed		3 (6%)	
Mediastinal, adenocarcinoma, metastatic, uterus	1 (2%)		
Mediastinal, histiocytic sarcoma	1 (2%)		
Mediastinal, lymphoma malignant lymphocytic	1 (2%)		
Mediastinal, lymphoma malignant			1 (2%)
Mediastinal, lymphoma malignant mixed	1 (2%)	4 (8%)	1 (2%)
Pancreatic, lymphoma malignant mixed		2 (4%)	1 (2%)
Renal, histiocytic sarcoma	1 (2%)		
Renal, lymphoma malignant			1 (2%)
Renal, lymphoma malignant mixed		4 (8%)	1 (2%)
Lymph node, mandibular	(48)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)		2 (4%)
Lymphoma malignant mixed	3 (6%)	3 (6%)	2 (4%)
Lymph node, mesenteric	(47)	*(50)	(45)
Histiocytic sarcoma	2 (4%)		
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)		3 (7%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	7 (15%)	5 (10%)	4 (9%)
Spleen	(50)	*(50)	(49)
Hemangiosarcoma	1 (2%)		1 (2%)
Hemangiosarcoma, metastatic, skin			1 (2%)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)	1 (2%)	5 (10%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	8 (16%)	7 (14%)	8 (16%)
Thymus	(47)	*(50)	(47)
Lymphoma malignant histiocytic	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)		1 (2%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	1 (2%)		2 (4%)

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

	Vehicle Control	300 mg/kg	600 mg/kg
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	*(50)	(49)
Adenocarcinoma	2 (4%)	2 (4%)	2 (4%)
Skin	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Papilloma squamous		1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)
Subcutaneous tissue, lymphoma malignant mixed, multiple			1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)		
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Adenocarcinoma, metastatic, mammary gland	1 (2%)		1 (2%)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Alveolar/bronchiolar adenoma		1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)		
Histiocytic sarcoma	2 (4%)		
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Lymphoma malignant lymphocytic	3 (6%)		2 (4%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	2 (4%)	2 (4%)	3 (6%)
Mediastinum, lymphoma malignant lymphocytic	2 (4%)		
Mediastinum, lymphoma malignant mixed		1 (2%)	
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)		
Lymphoma malignant mixed			1 (2%)
URINARY SYSTEM			
Kidney	(50)	*(50)	(49)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)		2 (4%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	3 (6%)		2 (4%)
Urinary bladder	(50)	*(50)	(48)
Leiomyosarcoma, metastatic, uterus	1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)		2 (4%)
Lymphoma malignant			1 (2%)
Lymphoma malignant mixed	1 (2%)		1 (2%)

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

	Vehicle Control	300 mg/kg	600 mg/kg
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant lymphocytic	4 (8%)	2 (4%)	6 (12%)
Lymphoma malignant mixed	8 (16%)	7 (14%)	8 (16%)
Lymphoma malignant histiocytic	1 (2%)		1 (2%)
Hemangiosarcoma	1 (2%)		2 (4%)
Lymphoma malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Moribund	11	13	7
Dead	7	8	9
Terminal sacrifice	30	27	34
Accidently killed	1	1	
Accident	1	1	
TUMOR SUMMARY			
Total animals with primary neoplasms **	29	23	28
Total primary neoplasms	44	29	38
Total animals with benign neoplasms	12	10	11
Total benign neoplasms	12	13	15
Total animals with malignant neoplasms	21	16	21
Total malignant neoplasms	32	16	23
Total animals with secondary neoplasms ***	4		2
Total secondary neoplasms	8		2

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

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

WEEKS ON STUDY	002	064	069	072	072	075	075	076	078	082	087	090	091	092	093	096	096	100	101	102	105	105	105	105	105
CARCASS ID	72 1	70 1	71 1	72 2	74 1	71 2	74 2	77 1	68 1	72 3	72 4	70 2	70 3	73 1	77 2	69 1	76 1	68 2	69 2	76 2	68 3	68 4	68 5	69 3	69 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+
Adenocarcinoma, metastatic, uterus												X													
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	M
Intestine small, ileum	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																X									
Hepatocellular adenoma																									
Histiocytic sarcoma																				X			X		
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X								X				
Lymphoma malignant mixed																									
Mesentery						+		+	+	+		+	+		+			+					+		+
Adenocarcinoma, metastatic, uterus												X													
Histiocytic sarcoma																							X		
Lymphoma malignant lymphocytic										X			X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymphoma malignant lymphocytic													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X			X												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X			X												
Tooth																				+					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pars distalis, adenoma																						X			X
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic													X												
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS		+																							
GENITAL SYSTEM																									
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Adenoma				X																					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X													
Histiocytic sarcoma																							X		
Lymphoma malignant lymphocytic										X			X												
Polyp stromal																									

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

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

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	695	704	705	713	714	715	725	732	733	734	735	743	744	745	751	752	753	754	755	763	764	765	773	774	775	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum *	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Adenocarcinoma, metastatic, uterus																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																			X							1
Histiocytic sarcoma																										2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X							X		X							X									4
Mesentery																				+						11
Adenocarcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed	X																									1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										2
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma															X									X	X	5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Follicular cell, adenoma																						X				1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										2
Polyp stromal										X																1

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

WEEKS ON STUDY	002	064	069	072	072	075	075	076	078	082	087	090	091	092	093	096	096	100	101	102	105	105	105	105	105
CARCASS ID	721	701	711	722	741	712	742	771	681	723	724	702	703	731	772	691	761	682	692	762	683	684	685	693	694
HEMATOPOIETIC SYSTEM																									
Blood																			+	+	+		+		
Lymphoma malignant lymphocytic																					X				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, adenocarcinoma, metastatic, mammary gland				X																					
Iliac, histiocytic sarcoma																				X					
Iliac, lymphoma malignant lymphocytic													X												
Mediastinal, adenocarcinoma, metastatic, uterus												X													
Mediastinal, histiocytic sarcoma																				X					
Mediastinal, lymphoma malignant lymphocytic													X												
Mediastinal, lymphoma malignant mixed																									
Renal, histiocytic sarcoma																				X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X												
Lymphoma malignant mixed																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+
Histiocytic sarcoma																				X			X		
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X	X											
Lymphoma malignant mixed																								X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X								X				
Lymphoma malignant mixed																								X	
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X												
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenocarcinoma				X															X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X															
Subcutaneous tissue, sarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Lymphoma malignant lymphocytic													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X			X												
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus												X													
Adenocarcinoma, metastatic, mammary gland				X																					
Carcinoma, metastatic, harderian gland																									
Histiocytic sarcoma																				X			X		
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic										X			X								X				
Lymphoma malignant mixed																									
Mediastinum, lymphoma malignant lymphocytic										X			X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenoma																									
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Lymphoma malignant lymphocytic										X			X												
Lymphoma malignant mixed																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus																							X		
Lymphoma malignant lymphocytic										X			X												
Lymphoma malignant mixed																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	695	704	705	713	714	715	725	732	733	734	735	743	744	745	751	752	753	754	755	763	764	765	773	774	775	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										4
Lymphoma malignant lymphocytic																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, adenocarcinoma, metastatic, mammary gland																										1
Iliac, histiocytic sarcoma																										1
Iliac, lymphoma malignant lymphocytic																										1
Mediastinal, adenocarcinoma, metastatic, uterus																										1
Mediastinal, histiocytic sarcoma																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig. mixed	X																									1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed	X																		X		X					3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	47
Histiocytic sarcoma																										2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X							X			X						X		X		X					7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X							X		X	X						X		X		X					8
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																	X									1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																										1
Adenocarcinoma, metastatic, mammary gland																										1
Carcinoma, metastatic, harderian gland												X														1
Histiocytic sarcoma																										2
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X									X																2
Mediastinum, lymphoma malignant lymphocytic																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland												+									+					2
Adenoma																					X					1
Carcinoma												X														1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed	X																X		X							3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma, metastatic, uterus																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed	X																									1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 300 mg/kg

WEEKS ON STUDY	015	057	062	066	068	070	077	078	080	085	088	088	090	090	092	095	095	096	097	101	102	102	103	105	105
CARCASS ID	901	911	951	971	891	931	921	932	915	952	892	933	881	953	972	941	954	942	961	902	903	882	883	884	885
ALIMENTARY SYSTEM																									
Intestine small																									
Intestine small, jejunum																									
Polyp adenomatous																									
Liver											+		+	+	+							+			
Hepatocellular carcinoma																									
Hepatocellular adenoma															X										
Hepatocellular adenoma, multiple																									
Lymphoma malignant mixed											X		X												
Mesentery														+								+	+		
Lymphoma malignant mixed																							X		
Salivary glands	+																								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Papilloma squamous										X				X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
None																									
ENDOCRINE SYSTEM																									
Pituitary gland												+													
Pars distalis, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary			+			+	+	+	+			+			+				+	+				+	+
Uterus		+								+		+			+		+				+	+	+	+	+
Leiomyoma																									
Lymphoma malignant mixed																							X		
Sarcoma stromal										X															
HEMATOPOIETIC SYSTEM																									
Blood																				+	+				
Lymph node			+				+			+	+	+	+			+							+		
Axillary, lymphoma malignant mixed											X					X							X		
Bronchial, lymphoma malignant mixed											X														
Iliac, lymphoma malignant mixed											X					X							X		
Inguinal, lymphoma malignant mixed											X					X							X		
Mediastinal, lymphoma malignant mixed											X		X			X							X		
Pancreatic, lymphoma malignant mixed											X														
Renal, lymphoma malignant mixed											X					X							X		
Lymph node, mandibular											+					+							+		
Lymphoma malignant mixed											X					X							X		
Lymph node, mesenteric											+		+			+							+		
Lymphoma malignant mixed											X		X			X							X		
Spleen	+		+				+				+	+	+			+			+		+		+		
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed											X		X			X							X		
INTEGUMENTARY SYSTEM																					+				
Mammary gland																					X				
Adenocarcinoma																									
Skin	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone													+												
Skeletal muscle																						+			
NERVOUS SYSTEM																									
Brain													+												
RESPIRATORY SYSTEM																									
Lung		+											+										+		
Alveolar/bronchiolar adenoma																									
Lymphoma malignant mixed													X										X		
Mediastinum, lymphoma malignant mixed													X												
SPECIAL SENSES SYSTEM																									
Harderian gland					+																				
Adenoma					X																				
URINARY SYSTEM																									
Kidney			+			+																			

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 300 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	893	894	895	904	905	912	913	914	922	923	924	925	934	935	943	944	945	955	962	963	964	965	973	974	975	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Intestine small					+																					1
Intestine small, jejunum					+																					1
Polyp adenomatous					X																					1
Liver		+				+							+													8
Hepatocellular carcinoma		X											X													2
Hepatocellular adenoma																										1
Hepatocellular adenoma, multiple						X																				1
Lymphoma malignant mixed																										2
Mesentery														+								+				5
Lymphoma malignant mixed																										1
Salivary glands																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																					X					1
Papilloma squamous					X									X								X				5
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
None																										
ENDOCRINE SYSTEM																										
Pituitary gland						+																		+		3
Pars distalis, adenoma																								X		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary												+	+									+				14
Uterus	+		+	+	+	+	+		+		+		+		+	+	+	+			+	+	+		+	+	29
Leiomyoma					X																					1
Lymphoma malignant mixed																										1
Sarcoma stromal			X																							2
HEMATOPOIETIC SYSTEM																										
Blood				+															+							4
Lymph node											+											+				10
Axillary, lymphoma malignant mixed																										3
Bronchial, lymphoma malignant mixed																										1
Iliac, lymphoma malignant mixed																										3
Inguinal, lymphoma malignant mixed																										3
Mediastinal, lymphoma malig. mixed																										4
Pancreatic, lymphoma malignant mixed											X															2
Renal, lymphoma malignant mixed											X															4
Lymph node, mandibular																										3
Lymphoma malignant mixed																										3
Lymph node, mesenteric											+															5
Lymphoma malignant mixed											X															5
Spleen				+	+	+					+			+	+							+		+		18
Lymphoma malignant lymphocytic															X											1
Lymphoma malignant mixed						X					X			X												7
INTEGUMENTARY SYSTEM																										
Mammary gland																			+							2
Adenocarcinoma																			X							2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous																				X						1
Subcutaneous tissue, fibrosarcoma				X																						1
MUSCULOSKELETAL SYSTEM																										
Bone																										1
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain																										1
RESPIRATORY SYSTEM																										
Lung						+																				4
Alveolar/bronchiolar adenoma						X																				1
Lymphoma malignant mixed																										2
Mediastinum, lymphoma malig. mixed																										1
SPECIAL SENSES SYSTEM																										
Harderian gland																										1
Adenoma																										1
URINARY SYSTEM																										
Kidney																										2

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE: 600 mg/kg

WEEKS ON STUDY	0 5 0	0 6 3	0 6 6	0 7 0	0 7 2	0 7 6	0 7 7	0 8 7	0 8 9	0 8 9	0 9 8	0 9 9	1 0 1	1 0 2	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	8 7 1	8 7 2	8 3 1	8 0 1	8 5 1	8 1 1	8 4 1	8 5 2	8 6 1	8 4 2	7 8 1	8 3 2	8 6 2	8 4 3	8 7 3	7 8 2	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 3	7 9 4	7 9 5	8 0 2
ALIMENTARY SYSTEM																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																X								
Hepatocellular adenoma																				X				
Lymphoma malignant lymphocytic														X										
Lymphoma malignant mixed									X		X		X											
Mesentery	+	+											+											
Lymphoma malignant mixed													X											
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X										
Lymphoma malignant mixed													X											
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X										
Lymphoma malignant mixed													X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X										
Papilloma squamous				X		X														X				
Squamous cell carcinoma																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X										
CARDIOVASCULAR SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X										
Lymphoma malignant mixed													X											
ENDOCRINE SYSTEM																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma															X								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
GENERAL BODY SYSTEM																								
None																								
GENITAL SYSTEM																								
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																								
Lymphoma malignant lymphocytic														X										
Lymphoma malignant										X														
Lymphoma malignant mixed													X											
Polyp stromal																							X	

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	803	804	805	812	813	814	815	821	822	823	824	825	833	834	835	844	845	853	854	855	863	864	865	874	875	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Hepatocellular adenoma									X				X		X											4
Lymphoma malignant lymphocytic						X																				2
Lymphoma malignant mixed		X	X																							5
Mesentery			+					+										+								6
Lymphoma malignant mixed			X					X																		3
Pancreas	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed			X																							2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Papilloma squamous	X								X				X													6
Squamous cell carcinoma																	(a) X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma										X																1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	44
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma							X																			1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant																										1
Lymphoma malignant mixed																										1
Polyp stromal																										1

(a) Diagnosis not confirmed by PWG or NTP pathologists. See Results p. 42.

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 mg/kg (Continued)

WEEKS ON STUDY	050	063	066	070	072	076	077	087	089	089	098	099	101	102	103	105	105	105	105	105	105	105	105	105
CARCASS ID	871	872	831	801	851	811	841	852	861	842	781	832	862	843	873	822	833	844	855	911	922	933	944	955	802
HEMATOPOIETIC SYSTEM																									
Blood													+	+											
Lymphoma malignant lymphocytic														X											
Lymphoma malignant mixed													X												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant mixed																									
Iliac, lymphoma malignant										X															
Iliac, lymphoma malignant mixed													X												
Mediastinal, lymphoma malignant										X															
Mediastinal, lymphoma malignant mixed													X												
Pancreatic, lymphoma malignant mixed																									
Renal, lymphoma malignant										X															
Renal, lymphoma malignant mixed													X												
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Lymphoma malignant mixed													X												
Lymph node, mesenteric	+	+	A	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X				X							
Lymphoma malignant										X															
Lymphoma malignant mixed													X												
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Hemangiosarcoma, metastatic, skin																									
Lymphoma malignant lymphocytic														X				X				X			
Lymphoma malignant										X															
Lymphoma malignant mixed									X		X		X							X					
Thymus	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Lymphoma malignant										X															
Lymphoma malignant mixed													X												
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X			X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									
Subcutaneous tissue, lymphoma malignant mixed, multiple													X												
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland												X													
Lymphoma malignant histiocytic											X														
Lymphoma malignant lymphocytic														X				X							
Lymphoma malignant										X															
Lymphoma malignant mixed									X				X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Harderian gland													+												
Adenoma																									
Lymphoma malignant mixed													X												
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant										X															
Lymphoma malignant mixed											X		X												
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic														X											
Lymphoma malignant										X															
Lymphoma malignant mixed													X												

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 600 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	803	804	805	812	813	814	815	821	822	823	824	825	833	834	835	844	845	853	854	855	863	864	865	874	875	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										2
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant mixed			X																							1
Iliac, lymphoma malignant																										1
Iliac, lymphoma malignant mixed																										1
Mediastinal, lymphoma malignant																										1
Mediastinal, lymphoma malig. mixed																										1
Pancreatic, lymphoma malignant mixed								X																		1
Renal, lymphoma malignant																										1
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																								X		2
Lymphoma malignant mixed								X																		2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Lymphoma malignant lymphocytic										X																3
Lymphoma malignant																										1
Lymphoma malignant mixed		X	X					X																		4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, skin										X																1
Lymphoma malignant lymphocytic						X																		X		5
Lymphoma malignant																										1
Lymphoma malignant mixed		X	X					X								X										8
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymphoma malignant lymphocytic																										1
Lymphoma malignant																										1
Lymphoma malignant mixed								X																		2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma										X																1
Subcutaneous tissue, lymphoma malignant mixed, multiple																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant																										1
Lymphoma malignant mixed			X																							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																									+	1
Harderian gland						+																				2
Adenoma						X																				1
Lymphoma malignant mixed																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic						X				X																2
Lymphoma malignant																										1
Lymphoma malignant mixed																										2
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic										X																2
Lymphoma malignant																										1
Lymphoma malignant mixed																										1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	300 mg/kg	600 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/50 (2%)	(b) 2/8 (25%)	4/49 (8%)
Adjusted Rates (c)	3.3%		11.4%
Terminal Rates (d)	1/30 (3%)		4/35 (11%)
Day of First Observation	729		729
Life Table Test (e)			P=0.227
Logistic Regression Test (e)			P=0.227
Fisher Exact Test (e)			P=0.175
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	(b) 4/8 (50%)	5/49 (10%)
Adjusted Rates (c)	6.1%		14.3%
Terminal Rates (d)	1/30 (3%)		5/35 (14%)
Day of First Observation	667		729
Life Table Test (e)			P=0.282
Logistic Regression Test (e)			P=0.261
Fisher Exact Test (e)			P=0.210
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	5/47 (11%)	(b) 1/3 (33%)	2/48 (4%)
Adjusted Rates (c)	17.2%		5.6%
Terminal Rates (d)	5/29 (17%)		1/34 (3%)
Day of First Observation	729		718
Life Table Test (e)			P=0.156N
Logistic Regression Test (e)			P=0.165N
Fisher Exact Test (e)			P=0.209N
Forestomach: Squamous Papilloma			
Overall Rates (f)	0/50 (0%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (c)	0.0%	15.6%	16.2%
Terminal Rates (d)	0/30 (0%)	3/27 (11%)	5/35 (14%)
Day of First Observation		591	526
Life Table Tests (e)	P=0.031	P=0.030	P=0.027
Logistic Regression Tests (e)	P=0.020	P=0.032	P=0.020
Cochran-Armitage Trend Test (e)	P=0.017		
Fisher Exact Test (e)		P=0.028	P=0.013
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	13/50 (26%)	(g) 9/50 (18%)	15/50 (30%)
Adjusted Rates (c)	36.9%	27.5%	37.2%
Terminal Rates (d)	9/30 (30%)	5/27 (19%)	10/35 (29%)
Day of First Observation	568	612	618
Life Table Tests (e)	P=0.522	P=0.307N	P=0.577
Logistic Regression Tests (e)	P=0.424	P=0.245N	P=0.475
Cochran-Armitage Trend Test (e)	P=0.364		
Fisher Exact Test (e)		P=0.235N	P=0.412

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Eighteen spleens and 10 lymph nodes were examined microscopically.

TABLE D4. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Southern Research Institute	
Ethyl acrylate	1/50
Benzyl acetate	0/50
Allyl isovalerate	1/50
HC Red No. 3	0/50
Chlorinated paraffins (C_{23}, 43% chlorine)	0/49
Allyl isothiocyanate	0/47
Geranyl acetate	0/50
C.I. Acid Orange 3	4/50
Chlorinated paraffins (C_{12}, 60% chlorine)	2/50
TOTAL	(b) 8/446 (1.8%)
SD (c)	2.73%
Range (d)	
High	4/50
Low	0/50
Overall Historical Incidence	
TOTAL	(e) 33/2,047 (1.6%)
SD (c)	2.76%
Range (d)	
High	(b) 5/44
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) All squamous cell papillomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 2 papillomas, NOS, 30 squamous cell papillomas, and 1 squamous cell carcinoma

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE

	Vehicle Control	300 mg/kg	600 mg/kg
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, rectum	(45)		(49)
Inflammation, chronic	1 (2%)		
Liver	(50)	(8)	(49)
Focal cellular change	1 (2%)		
Hematopoietic cell proliferation, multifocal	2 (4%)		4 (8%)
Hemorrhage, multifocal	2 (4%)		
Necrosis, multifocal	3 (6%)		2 (4%)
Vacuolization cytoplasmic, diffuse	1 (2%)	1 (13%)	
Vacuolization cytoplasmic, focal		1 (13%)	
Centrilobular, necrosis	1 (2%)		
Sinusoid, infiltration cellular, polymorphonuclear	5 (10%)		1 (2%)
Mesentery	(11)	(5)	(6)
Abscess	1 (9%)		1 (17%)
Inflammation, suppurative, acute	4 (36%)		2 (33%)
Fat, necrosis, focal	2 (18%)	3 (60%)	1 (17%)
Fat, necrosis, multifocal		1 (20%)	
Salivary glands	(49)	(1)	(49)
Hemorrhage		1 (100%)	
Stomach, forestomach	(50)	(50)	(50)
Cyst			1 (2%)
Hyperplasia, focal	10 (20%)	15 (30%)	18 (36%)
Hyperplasia, lymphoid		1 (2%)	
Hyperplasia, multifocal	2 (4%)	8 (16%)	21 (42%)
Inflammation, subacute, focal		1 (2%)	
Inflammation, suppurative, acute, focal	4 (8%)	7 (14%)	4 (8%)
Inflammation, suppurative, acute, multifocal		1 (2%)	3 (6%)
Mineralization		1 (2%)	
Ulcer	2 (4%)	1 (2%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)
Mineralization	1 (2%)		
Tooth	(1)		
Dysplasia	1 (100%)		
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)		(50)
Cyst	2 (4%)		
Degeneration, fatty, focal			1 (2%)
Hyperplasia, focal	1 (2%)		
Hypertrophy, focal			1 (2%)
Spindle cell, hyperplasia	1 (2%)		
Adrenal gland, medulla	(50)		(50)
Hyperplasia, focal	2 (4%)		1 (2%)
Bilateral, infiltration cellular, polymorphonuclear			1 (2%)
Parathyroid gland	(42)		(47)
Cyst			1 (2%)
Pituitary gland	(47)	(3)	(48)
Pars distalis, angiectasis	1 (2%)		4 (8%)
Pars distalis, cyst	1 (2%)		
Pars distalis, hyperplasia, focal	3 (6%)	1 (33%)	4 (8%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
ENDOCRINE SYSTEM (Continued)			
Thyroid gland	(49)		(49)
C-cell, hyperplasia, focal	1 (2%)		
Follicle, cyst			3 (6%)
Follicle, degeneration, cystic			4 (8%)
Follicular cell, hyperplasia, focal	2 (4%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(47)	(14)	(44)
Abscess	4 (9%)	6 (43%)	1 (2%)
Abscess, multiple	4 (9%)	2 (14%)	6 (14%)
Cyst	10 (21%)	6 (43%)	9 (20%)
Inflammation, chronic			1 (2%)
Uterus	(50)	(29)	(50)
Hydrometria	6 (12%)	6 (21%)	4 (8%)
Hyperplasia, cystic	45 (90%)	27 (93%)	39 (78%)
Inflammation, suppurative, acute	6 (12%)	2 (7%)	6 (12%)
HEMATOPOIETIC SYSTEM			
Blood	(4)	(4)	(2)
Leukocytosis		1 (25%)	
Polychromasia	3 (75%)		
Bone marrow	(50)		(50)
Myelofibrosis	2 (4%)		2 (4%)
Myeloid cell, hyperplasia			2 (4%)
Lymph node	(50)	(10)	(50)
Bronchial, inflammation, suppurative, acute			1 (2%)
Deep cervical, hyperplasia			1 (2%)
Iliac, ectasia	1 (2%)		
Iliac, hyperplasia		3 (30%)	1 (2%)
Iliac, inflammation, suppurative, acute		1 (10%)	
Mediastinal, hyperplasia	1 (2%)	1 (10%)	
Mediastinal, inflammation, suppurative, acute	1 (2%)		1 (2%)
Renal, hyperplasia	4 (8%)	2 (20%)	2 (4%)
Lymph node, mandibular	(48)	(3)	(47)
Angiectasis	1 (2%)		
Hyperplasia	4 (8%)		1 (2%)
Lymph node, mesenteric	(47)	(5)	(45)
Angiectasis	1 (2%)		1 (2%)
Hyperplasia	2 (4%)		2 (4%)
Spleen	(50)	(18)	(49)
Atrophy		1 (6%)	
Fibrosis, focal			1 (2%)
Hematopoietic cell proliferation	13 (26%)	8 (44%)	7 (14%)
Hemorrhage, focal			1 (2%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)
Hyperplasia, lymphoid, focal		1 (6%)	
Necrosis, focal	1 (2%)		1 (2%)
Thymus	(47)		(47)
Atrophy	2 (4%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(2)	(49)
Duct, cyst	4 (8%)		3 (6%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZALDEHYDE (Continued)

	Vehicle Control	300 mg/kg	600 mg/kg
INTEGUMENTARY SYSTEM (Continued)			
Skin	(50)	(48)	(50)
Subcutaneous tissue, hemorrhage		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(1)	(50)
Cranium, hypertrophy, focal		1 (100%)	
NERVOUS SYSTEM			
Brain	(50)	(1)	(50)
Compression	1 (2%)	1 (100%)	
Hemorrhage, multifocal	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(4)	(50)
Congestion	1 (2%)		
Hemorrhage, multifocal	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, lymphoid, focal	1 (2%)		
Pigmentation, hemosiderin	1 (2%)		
Alveolar epithelium, hyperplasia, focal	2 (4%)		
Mediastinum, inflammation, suppurative, acute	3 (6%)		1 (2%)
Nose	(50)		(50)
Foreign body	1 (2%)		2 (4%)
Fungus			1 (2%)
Inflammation, suppurative, acute	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, subacute			1 (2%)
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(2)	(49)
Hydronephrosis	2 (4%)		
Metaplasia, osseous, focal			1 (2%)
Capsule, inflammation, suppurative, acute			1 (2%)
Glomerulus, inflammation, chronic	2 (4%)		1 (2%)
Papilla, necrosis	1 (2%)		
Renal tubule, atrophy, multifocal			1 (2%)
Renal tubule, degeneration, multifocal			2 (4%)
Renal tubule, dilatation, multifocal	3 (6%)		1 (2%)
Renal tubule, nuclear alteration, multifocal			2 (4%)
Renal tubule, regeneration, multifocal	2 (4%)		2 (4%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. 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 are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

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

Results

Results are presented in Table E1.

TABLE E1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	5/10	KRV
12	--	None positive
18	2/9	*M. pul.* (b)
24	--	None positive
MICE		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers.
(b) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX F

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

Pellet Diet: November 1981 to December 1983

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.59 ± 0.94	22.2-26.3	26
Crude fat (percent by weight)	4.96 ± 0.52	3.3-5.7	26
Crude fiber (percent by weight)	3.39 ± 0.52	2.9-5.6	26
Ash (percent by weight)	6.51 ± 0.49	5.7-7.3	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,084 ± 4,821	3,600-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.9 ± 2.42	12.0-21.0	26
Riboflavin (ppm)	7.6 ± 0.85	7.58-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.30 ± 0.13	1.11-1.63	26
Phosphorus (percent)	0.97 ± 0.05	0.88-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.52 ± 0.13	0.29-0.77	26
Cadmium (ppm) (a)	<0.10		26
Lead (ppm)	0.76 ± 0.62	0.33-3.37	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	8.66 ± 4.47	0.10-22.0	26
Nitrite nitrogen (ppm) (b)	2.16 ± 1.97	0.10-7.20	26
BHA (ppm) (c)	4.63 ± 4.74	2.0-17.0	26
BHT (ppm) (c)	2.67 ± 2.58	0.9-12.0	26
Aerobic plate count (CFU/g) (d)	41,212 ± 34,610	4,900-130,000	26
Coliform (MPN/g) (e)	48.42 ± 123	3.0-460	26
E. coli (MPN/g) (a)	<3.0		26
Total nitrosamines (ppb) (f)	5.25 ± 5.80	1.7-30.9	26
N-Nitrosodimethylamine (ppb) (f)	4.12 ± 5.83	0.8-30.0	26
N-Nitrosopyrrolidine (ppb) (f)	1.13 ± 0.46	0.81-2.9	26
Pesticides (ppm)			
α-BHC (a,g)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC-Lindane (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (a)	<0.05		26
Dieldrin (a)	<0.01		26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (h)	0.10 ± 0.09	0.05-0.45	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		25
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Thirteen batches contained more than 0.05 ppm.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF BENZALDEHYDE FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Benzaldehyde

Benzaldehyde (USP-grade) was obtained in two lots (Table G1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the benzaldehyde studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as benzaldehyde by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared and nuclear magnetic resonance spectra (Figures G1-G4) were consistent with those expected for the structure and with literature spectra (Sadtler Standard Spectra). The ultraviolet/visible spectra were consistent with that expected for the structure of benzaldehyde.

The purity of both lots of the study chemical was determined by elemental analysis, Karl Fischer water analysis, reaction of the carbonyl group with hydroxylammonium chloride in the presence of 2-dimethylaminoethanol and back-titration with perchloric acid of the excess hydroxylamine, titration with sodium hydroxide to determine free acid content (as benzoic acid), and gas chromatography. Gas chromatography was performed with flame ionization detection, a nitrogen carrier, a 20% SP2100/0.1% Carbowax 1500 column (system 1) or a 10% Carbowax 20M-TPA column (system 2).

Results of elemental analysis of lot no. JE5718HE for carbon and hydrogen were in agreement with the theoretical values. This lot contained 0.21% water by Karl Fischer analysis. Reaction of the carbonyl group indicated 99.5% purity. Free acid content as benzoic acid was 0.38%. Gas chromatography by system 1 indicated one impurity, with an area 0.23% of the major peak area. Gas chromatography with system 2 showed only the major peak, and no impurities were observed with areas greater or equal to 0.1% of the major peak area.

Results of elemental analysis of lot no. 005-0120 for carbon and hydrogen were in agreement with the theoretical values. This lot contained 0.24% water by Karl Fischer analysis. Titration of the carbonyl group indicated 97.8% purity. Free acid content as benzoic acid was 0.38%. Gas chromatography by both systems showed only the major peak and detected no impurities with areas greater than or equal to 0.1% of the major peak area.

TABLE G1. IDENTITY AND SOURCE OF BENZALDEHYDE USED IN THE GAVAGE STUDIES

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers		
JE5718HE	JE5718HE	JE5718HE; 005-0120
Date of Initial Use		
1/26/81	4/1/81	Lot no. 005-0120--06/16/83
Supplier		
Aldrich Chemical Co. (Milwaukee, WI)	Aldrich Chemical Co. (Milwaukee, WI)	Lot no. JE5718HE--Aldrich Chemical Co. (Milwaukee, WI); lot no. 005-0120--R.W. Greeff (Old Greenwich, CT)

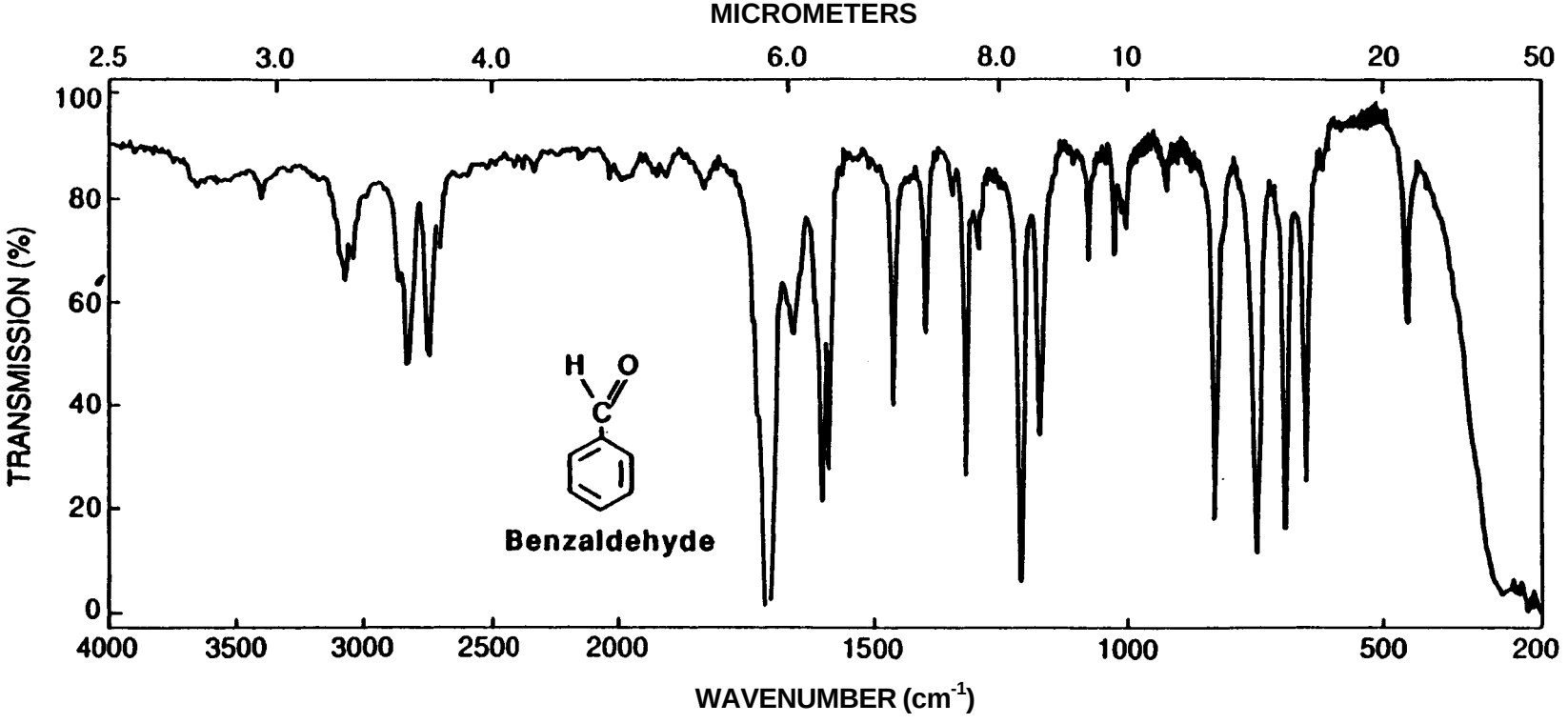


FIGURE G1. INFRARED ABSORPTION SPECTRUM OF BENZALDEHYDE (LOT NO. JE5718HE)

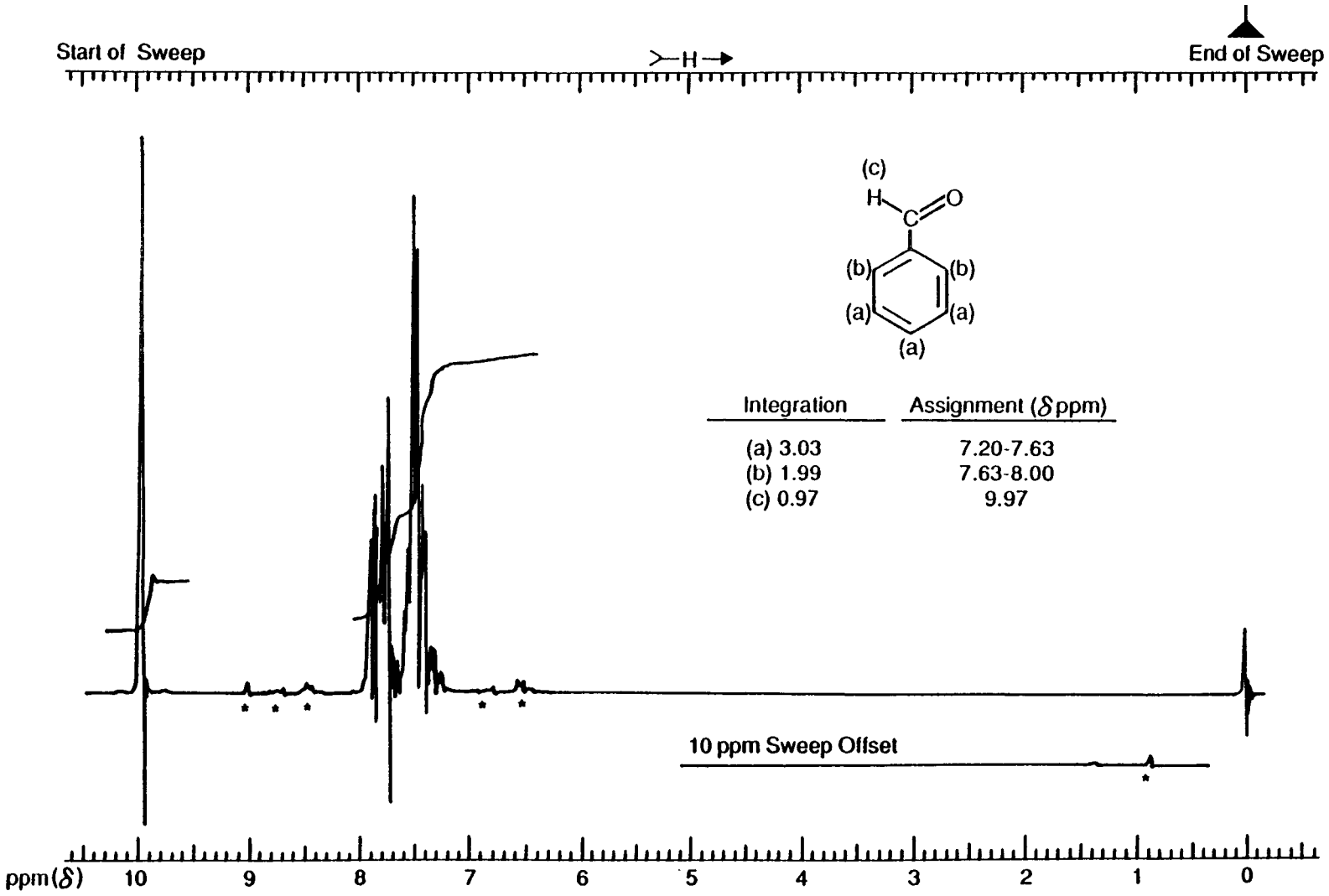


FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BENZALDEHYDE (LOT NO. JE5718HE)

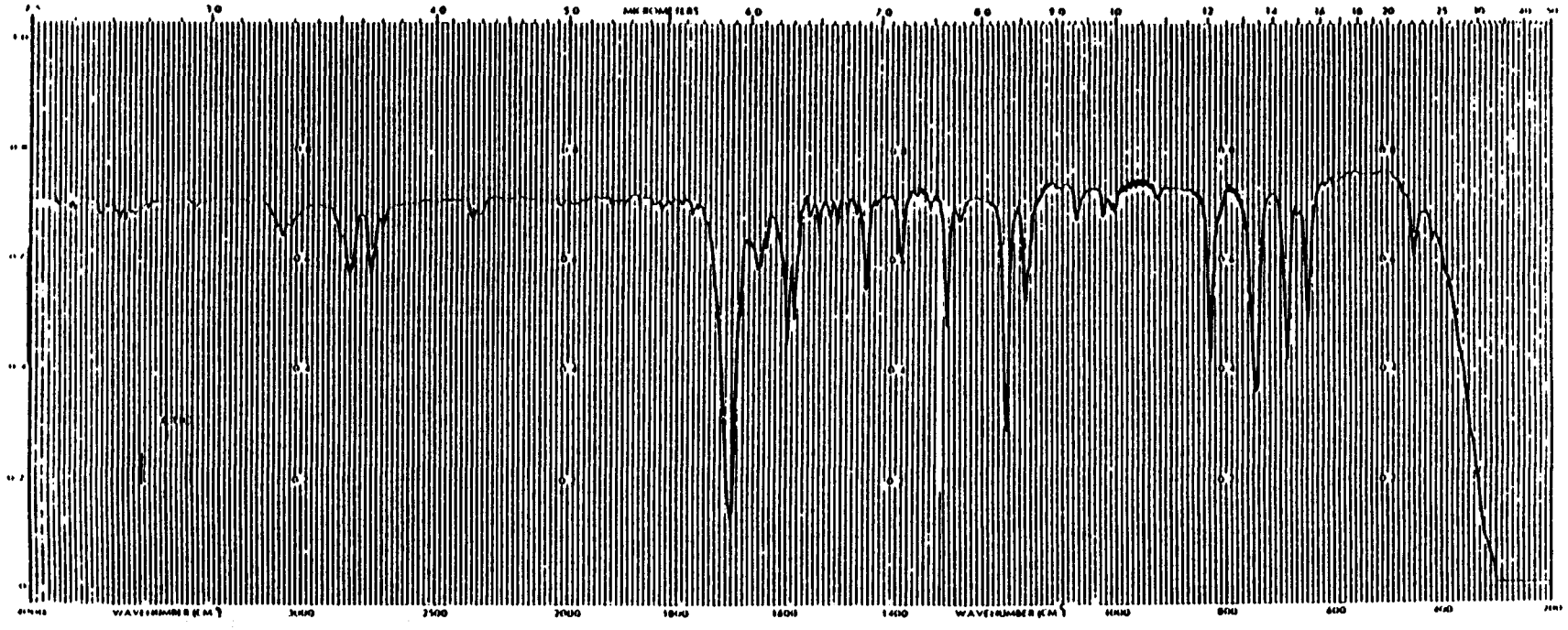


FIGURE G3. INFRARED ABSORPTION SPECTRUM OF BENZALDEHYDE (LOT NO. 005-0120)

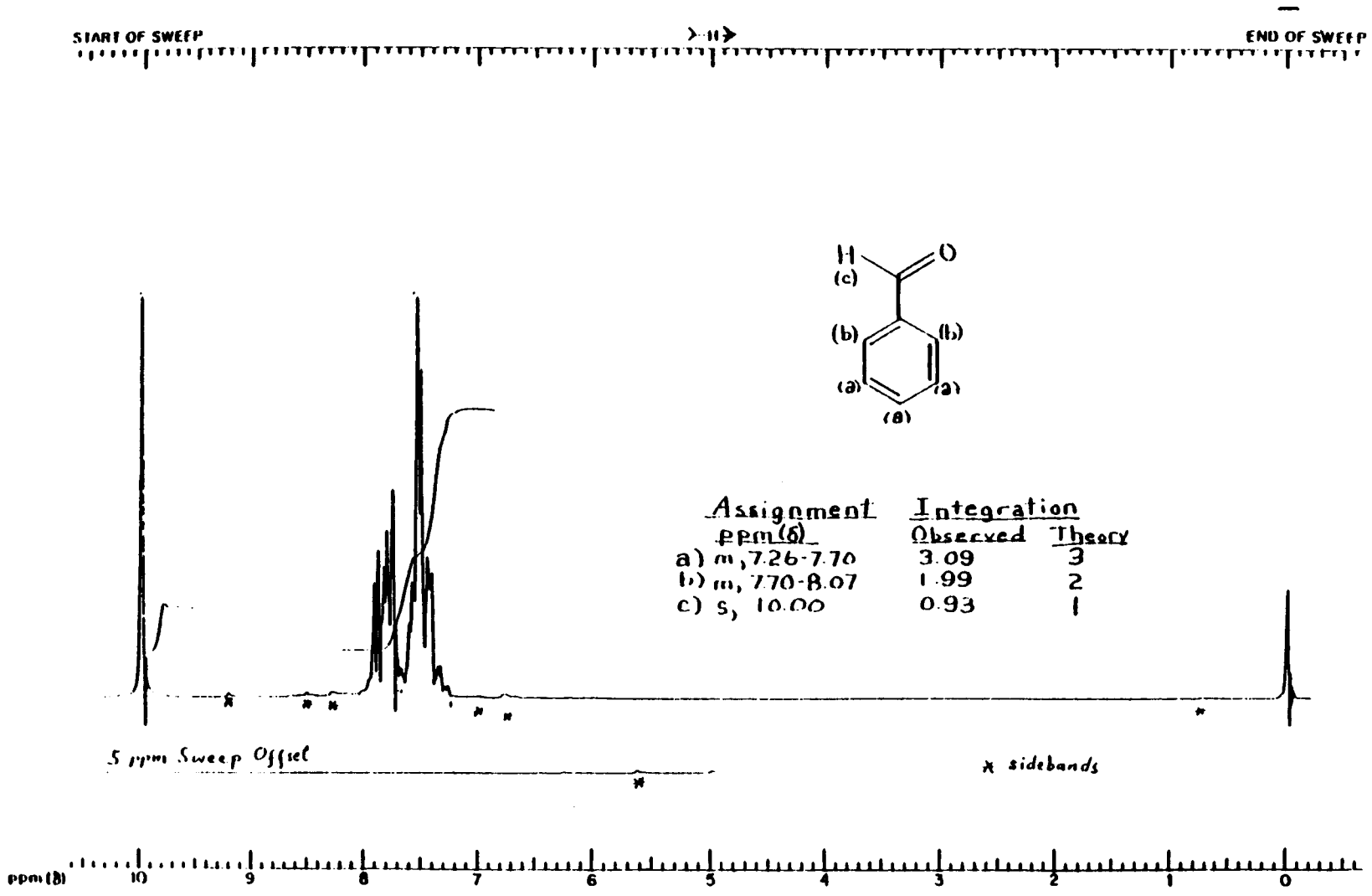


FIGURE G4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BENZALDEHYDE (LOT NO. 005-0120)

Benzaldehyde stability studies performed by gas chromatography with the same column as that described for system 2 and with 0.3% hexadecane in methylene chloride as an internal standard indicated that benzaldehyde was stable for 2 weeks when stored, protected from light, at temperatures up to 25° C. Slight decomposition was observed when benzaldehyde was stored at 60° C for 2 weeks. Refrigeration was recommended. Containers were repackaged into amber glass bottles that were flushed with nitrogen and stored at 5° C sealed in plastic containers. Periodic analysis by gas chromatography and titration of the free acid indicated no deterioration during the studies. The identity of the study chemical was confirmed by infrared analysis on lot no. JE5718HE 4 months after receipt at the study laboratory and on lot no. 005-0120 after receipt at the study laboratory.

Preparation and Characterization of Dose Formulations

The appropriate amounts of benzaldehyde and corn oil were mixed to give the desired concentrations (Table G2). Containers were flushed with nitrogen, and dose formulations were kept under nitrogen. For the 16-day studies, solutions were prepared weight to volume; for the 13-week and 2-year studies, mixtures were prepared volume to weight. The stability of benzaldehyde in corn oil was determined by gas chromatography with a 1% SP1000 column (after the sample was extracted with methanol), with anisole as an internal standard, and with flame ionization detection. Benzaldehyde dissolved in corn oil at about 80 mg/ml was found to be stable at room temperature in the dark for 14 days when stored in sealed vials. A small (approximately 5%) loss occurred when benzaldehyde in corn oil was exposed to air and light for 3 hours at room temperature. Dose formulations were stored in the dark at room temperature under nitrogen for no more than 14 days throughout the studies.

Periodic analysis of prepared benzaldehyde corn oil dose formulations was conducted at the study laboratory and the analytical chemistry laboratory. During the 13-week studies, dose formulations were analyzed two times, and the concentration of benzaldehyde in corn oil was determined by ultraviolet/visible spectrometry.

TABLE G2. PREPARATION AND STORAGE OF DOSE FORMULATIONS IN THE GAVAGE STUDIES OF BENZALDEHYDE

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate weight of chemical added to an aspirator bottle. A specified volume of corn oil was added with a stir bar. Bottle was flushed with nitrogen, covered with aluminum foil, and stirred 3 min. Solution was poured into an amber serum bottle, flushed with nitrogen, and capped	Specified volume of chemical added to appropriate weight of corn oil in a beaker with stirring. Beaker was covered with aluminum foil and stirred 1-2 min longer. Solution was poured into an amber serum bottle, flushed with nitrogen, and capped	Same as 13-wk studies
Maximum Storage Time		
2 wk	13 d	2 wk
Storage Conditions		
Under nitrogen at room temperature in the dark	Under nitrogen at room temperature in the dark	Under nitrogen at room temperature in the dark

APPENDIX G. CHEMICAL CHARACTERIZATION

During the 13-week studies, all dose formulations were found to be within ±10% of the target concentrations by the study laboratory (Table G3). The referee laboratory analyzed one dose formulation and found it to be within specifications.

During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals. The formulations were within ±10% of the target concentrations approximately 96% (77/80) of the time throughout the studies (Table G4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table G5).

TABLE G3. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZALDEHYDE

Date Mixed	Concentration of Benzaldehyde in Corn Oil (mg/g)		Determined as a Percent of Target
	Target	Determined (a)	
03/25/81	8.16	8.39	103
	10.88	11.2	103
	16.32	16.1	99
	21.76	22.0	101
	32.64	32.3	99
	43.53	45.4	104
	65.29	66.8	102
	87.05	85.2	98
	130.58	135.2	104
	174.1	178.9	103
05/13/81	8.16	8.5	104
	10.88	11.2	103
	16.32	17.0	104
	21.76	22.6	104
	32.64	34.4	105
	43.53	45.6	105
	65.29	69.8	107
	87.05	90.7	104
	130.58	140.8	108
	174.1	186.8	107
	43.53	(b) 42.5	97.6

(a) Results of duplicate analysis
(b) Referee analysis; results of triplicate analysis.

TABLE G4. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

Date Mixed	Concentration of Benzaldehyde in Corn Oil for Target Concentration (mg/g) (a)				
	21.8	32.6	43.5	65.3	87.1
01/07/82	23.1	(b) 36.4	47.4	68.4	
01/12/82		(c) 33.0			
03/04/82	22.6	34.0	45.0	66.6	
			44.3		84.4
04/29/82	22.2	33.8	44.4	63.3	
			44.4		88.8
06/24/82	22.7	33.6	44.4	70.7	
			44.8		90.6
08/19/82	21.6	32.8	43.4	65.0	
			43.2		89.0
10/14/82	21.8	33.0	43.6	67.5	
			43.8		89.7
12/09/82	23.4	32.9	43.4	65.4	
			45.6		(b) 102
12/14/82					(d) 101
12/16/82					(c) 84.5
02/03/83	19.8	31.4	43.6	(b) 45.6	
			46.3		83.2
02/08/83				(c) 67.7	
03/31/83	21.8	32.8	43.7	65.2	
			44.2		87.4
05/26/83	22.4	34.0	44.8	66.9	
			44.2		86.6
07/21/83	21.2	31.2	43.4	65.0	
			42.4		87.8
09/15/83	23.5	34.2	44.8	65.5	
			45.1		86.2
11/10/83	21.5	32.6	43.2	65.0	
			43.3		86.6
01/05/84	22.1	34.0	44.3	66.4	
Mean (mg/g)	22.1	33.3	44.3	64.8	88.5
Standard deviation	0.97	1.29	1.06	5.80	4.74
Coefficient of variation (percent)	4.4	3.8	2.4	9.0	5.3
Range (mg/g)	19.8-23.5	31.2-36.4	42.4-47.4	45.6-70.7	83.2-102.0
Number of samples	14	14	26	14	12

(a) Results of duplicate analysis
(b) Out of specifications; not used in studies.
(c) Remix; not included in the mean.
(d) Remix out of specifications; not used in studies; not included in the mean.

TABLE G5. RESULTS OF REFEREE ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF BENZALDEHYDE

Date Mixed	Target Concentration (mg/g)	Determined Concentration (mg/g)	
		Study Laboratory (a)	Referee Laboratory (b)
03/04/82	87.1	84.4	82.9
10/14/82	21.8	21.8	21.8
03/31/83	32.6	32.8	32.8
09/15/83	87.1	86.2	85.8

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

APPENDIX H

GENETIC TOXICOLOGY

OF BENZALDEHYDE

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983). Chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA102, TA104, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male F344 rat, B6C3F$_1$ mouse, or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 3.3 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by McGregor et al. (1990) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 800 µg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 1.6 mg/ml.

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

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

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

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

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

Drosophila Melanogaster Protocol: The assays for gene mutation and chromosomal translocation induction were performed as described by Woodruff et al. (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). Initially, study chemicals were assayed in the

sex-linked recessive lethal (SLRL) test by feeding to adult Canton-S wild-type males that were no more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) by using the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament and the tip is broken off to allow delivery of the test solution. Injection is either done manually by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution to slightly distend the abdomen of the fly (0.2-0.3 µl) or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of double-stick tape; injection into the thorax under the wing is performed with the aid of a dissecting microscope.

Toxicity tests attempted to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, exposure by feeding was done by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated as successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and then were placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. At least two experiments were performed for each study chemical, resulting in the testing of some 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was run.

Recessive lethal data were analyzed by the normal test (Margolin et al., 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

RESULTS

Benzaldehyde was not mutagenic to *S. typhimurium* strains TA100, TA1535, TA1537, or TA98 when tested according to a preincubation protocol with doses up to 1,000 µg/plate (slight toxicity noted at this dose) in both the presence and absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Haworth et al., 1983; Table H1). Results of *S. typhimurium* mutagenicity tests performed in a second laboratory with benzaldehyde doses of up to 3,333 µg/plate in strains TA100, TA102, and TA104 with and without induced rat or mouse liver S9 were also negative (Table H1). Benzaldehyde gave a positive response in the absence of exogenous metabolic activation for induction of trifluorothymidine resistance in mouse L5178Y/TK cells at the highest dose tested in each of two trials; no tests were performed with activation (McGregor et al., 1990; Table H2). In cytogenetic tests with CHO cells, benzaldehyde induced SCEs at doses of 50 and 160 µg/ml in the absence of S9 and at a dose of 1,600 µg/ml in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Galloway et al., 1987; Table H3). No induction of chromosomal aberrations was observed in CHO cells treated with up to 500 µg/ml benzaldehyde in the absence of S9 or with up to 1,600 µg/ml with S9 (Galloway et al., 1987; Table H4). No significant induction of sex-linked recessive lethal mutations was observed in the germ cells of male *D. melanogaster* administered benzaldehyde at a concentration of 1,150 ppm by feeding or 2,500 ppm by injection (Woodruff et al., 1985; Table H5).

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

Strain	Dose (µg/plate)	Revertants/Plate (b)					
TA102 (c)		−S9		+10% S9 (mouse)		+10% S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	243 ± 6.9	213 ± 1.5	267 ± 17.4	232 ± 16.2	263 ± 9.3	202 ± 1.3
	33	300 ± 16.0	183 ± 9.6	246 ± 26.5	244 ± 19.5	264 ± 23.8	210 ± 5.0
	100	273 ± 4.3	195 ± 16.5	215 ± 0.0	244 ± 16.1	234 ± 10.6	210 ± 5.5
	333	227 ± 12.2	179 ± 11.4	255 ± 24.1	244 ± 14.2	250 ± 12.3	205 ± 2.3
	1,000	254 ± 8.7	168 ± 8.8	212 ± 4.2	178 ± 5.4	281 ± 7.2	195 ± 15.5
	(d) 3,333	69 ± 10.2	42 ± 5.3	99 ± 9.5	133 ± 6.2	70 ± 9.3	102 ± 7.3
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (e)	1,422 ± 52.4	1,142 ± 183.3	446 ± 8.0	392 ± 8.0	530 ± 37.9	373 ± 10.8
TA104 (c)		−S9		+S9 (mouse)		+S9 (rat)	
				Trial 1	Trial 2	Trial 1	Trial 2
	0	275 ± 9.2		362 ± 9.3	447 ± 14.4	452 ± 9.6	382 ± 12.3
	33	301 ± 11.5		345 ± 20.5	467 ± 12.2	437 ± 12.5	395 ± 28.1
	100	313 ± 12.3		417 ± 14.6	394 ± 48.8	437 ± 17.6	347 ± 18.2
	333	281 ± 21.9		352 ± 29.6	387 ± 5.5	412 ± 19.2	366 ± 24.8
	1,000	274 ± 9.6		320 ± 11.9	369 ± 17.1	358 ± 35.8	399 ± 8.6
	(d) 3,333	72 ± 8.5		256 ± 19.2	338 ± 6.8	246 ± 14.5	250 ± 0.9
	Trial summary	Negative		Negative	Negative	Negative	Negative
	Positive control (e)	609 ± 39.8		724 ± 19.9	626 ± 27.8	1,031 ± 88.4	544 ± 27.2
TA100 (c)		−S9		+S9 (mouse)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	84 ± 1.9	87 ± 4.4	101 ± 7.0	94 ± 4.9	100 ± 6.7	113 ± 11.1
	33	81 ± 3.3	94 ± 4.5	103 ± 8.5	101 ± 7.8	103 ± 4.0	106 ± 8.4
	100	82 ± 3.4	96 ± 1.5	100 ± 1.5	77 ± 2.3	98 ± 11.1	124 ± 5.0
	333	80 ± 9.0	79 ± 5.5	102 ± 4.8	96 ± 7.2	93 ± 7.0	119 ± 3.8
	1,000	90 ± 2.3	87 ± 0.7	86 ± 1.2	88 ± 1.9	98 ± 9.2	88 ± 4.0
	(d) 3,333	2 ± 1.2	66 ± 4.9	70 ± 6.0	81 ± 1.5	24 ± 7.5	87 ± 10.6
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (e)	253 ± 5.2	439 ± 20.4	2,071 ± 19.1	661 ± 81.6	899 ± 35.4	219 ± 17.9
TA100 (f)		−S9		+10% S9 (hamster)		+10% S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
	0	143 ± 13.1	132 ± 16.4	80 ± 3.8	117 ± 6.0	148 ± 5.4	123 ± 1.9
	10	135 ± 11.1	127 ± 4.7	83 ± 4.9	103 ± 5.2	142 ± 5.8	115 ± 4.6
	33	130 ± 6.0	118 ± 4.7	116 ± 6.4	111 ± 2.7	134 ± 3.1	122 ± 3.9
	100	123 ± 10.0	105 ± 5.0	81 ± 5.6	96 ± 4.1	131 ± 1.7	115 ± 2.5
	333	120 ± 1.2	(d) 108 ± 6.5	87 ± 3.6	103 ± 10.1	132 ± 5.7	125 ± 11.4
	(d) 1,000	120 ± 0.9	102 ± 5.6	81 ± 1.3	90 ± 3.7	128 ± 0.6	116 ± 11.4
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (e)	2,226 ± 29.7	2,124 ± 65.5	757 ± 25.5	1,044 ± 8.1	431 ± 28.8	745 ± 6.9

TABLE H1. MUTAGENICITY OF BENZALDEHYDE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+10% S9 (hamster)		+10% S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA1535 (f)	0	32 ± 4.0	19 ± 4.4	10 ± 3.0	8 ± 2.2	14 ± 1.7	9 ± 0.3
	10	30 ± 3.9	22 ± 0.7	11 ± 1.3	10 ± 3.8	10 ± 1.2	9 ± 1.5
	33	26 ± 0.6	30 ± 4.4	15 ± 2.0	9 ± 2.3	8 ± 3.1	9 ± 2.2
	100	28 ± 3.2	18 ± 4.1	9 ± 0.7	10 ± 2.9	14 ± 0.6	9 ± 1.5
	333	24 ± 1.0	21 ± 2.0	8 ± 1.5	11 ± 2.1	12 ± 2.0	10 ± 0.9
	1,000	(d) 19 ± 3.2	(d) 20 ± 2.7	(d) 9 ± 1.7	11 ± 1.5	(d) 15 ± 2.0	11 ± 2.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (e)		1,984 ± 31	1,886 ± 58.5	108 ± 7.7	97 ± 12.7	47 ± 11.1	62 ± 4.4
TA1537 (f)	0	16 ± 1.5	7 ± 1.7	12 ± 0.0	8 ± 0.9	13 ± 3.1	6 ± 0.7
	10	11 ± 0.6	6 ± 0.9	13 ± 1.2	7 ± 1.3	16 ± 4.2	7 ± 2.6
	33	14 ± 3.3	7 ± 0.7	15 ± 1.9	7 ± 0.9	16 ± 2.8	7 ± 1.3
	100	14 ± 2.7	7 ± 0.7	11 ± 2.0	7 ± 1.5	13 ± 1.7	7 ± 3.3
	333	13 ± 2.1	8 ± 1.9	14 ± 0.7	10 ± 0.9	15 ± 0.7	4 ± 0.3
	1,000	(d) 7 ± 1.5	6 ± 1.5	12 ± 0.9	(d) 6 ± 1.9	15 ± 4.4	(d) 6 ± 2.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (e)		765 ± 57.2	303 ± 36.3	149 ± 6.5	125 ± 17.0	59 ± 5.0	62 ± 4.6
TA98 (f)	0	21 ± 2.3	20 ± 1.0	31 ± 4.0	30 ± 4.0	37 ± 1.0	27 ± 1.5
	10	26 ± 0.3	23 ± 4.1	30 ± 3.1	23 ± 4.0	33 ± 3.7	21 ± 3.7
	33	28 ± 3.0	22 ± 2.3	33 ± 5.2	23 ± 3.6	36 ± 1.2	21 ± 2.1
	100	21 ± 2.2	19 ± 2.8	38 ± 1.5	22 ± 3.0	33 ± 3.5	30 ± 2.9
	333	26 ± 2.0	15 ± 1.7	27 ± 1.5	30 ± 2.1	29 ± 1.9	30 ± 4.0
	1,000	26 ± 1.2	17 ± 4.8	27 ± 1.8	(d) 20 ± 2.3	28 ± 2.3	22 ± 3.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (e)		2,228 ± 34.5	1,865 ± 27.7	1,763 ± 47.0	1,032 ± 55.6	925 ± 17.3	580 ± 13.3

(a) The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster, F344 rat, or B6C3F$_1$ mouse liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Study performed at Inveresk Research International
(d) Slight toxicity
(e) Positive control; 2-aminoanthracene was used with all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.
(f) Study performed at EG&G Mason Research Institute

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY BENZALDEHYDE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
– S9					
Trial 1					
Dimethyl sulfoxide		74.3 ± 8.2	99.7 ± 2.6	114.3 ± 7.7	52.0 ± 2.6
Benzaldehyde	(d) 50	66.0 ± 6.0	96.5 ± 4.5	98.5 ± 6.5	50.0 ± 1.0
	100	85.0 ± 5.0	102.0 ± 1.0	130.0 ± 6.0	51.0 ± 0.0
	200	69.5 ± 10.5	79.5 ± 14.5	125.5 ± 4.5	61.5 ± 7.5
	400	73.0 ± 5.0	55.0 ± 4.0	403.5 ± 2.5	(e) 185.5 ± 14.5
	800	Lethal	--	--	--
Methyl methanesulfonate	(d) 15	49.5 ± 4.5	29.5 ± 2.5	365.5 ± 26.5	(e) 247.0 ± 7.0
Trial 2					
Dimethyl sulfoxide (f)		70.0 ± 3.6	100.0 ± 5.5	109.8 ± 2.0	53.0 ± 3.3
Benzaldehyde	80	75.0 ± 9.2	81.0 ± 6.4	108.0 ± 20.1	47.3 ± 3.7
	160	78.3 ± 6.7	77.3 ± 1.8	134.7 ± 18.8	56.7 ± 3.4
	320	81.0 ± 5.5	36.0 ± 3.1	171.0 ± 6.8	71.0 ± 6.8
	480	65.0 ± 9.3	13.3 ± 2.0	186.3 ± 10.1	(e) 98.0 ± 8.7
	640	Lethal	--	--	--
Methyl methanesulfonate	(d) 15	19.5 ± 1.5	13.5 ± 1.5	181.5 ± 5.5	(e) 314.5 ± 17.5

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by McGregor et al. (1990) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate, unless otherwise specified; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

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

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

(d) Data presented are the average of two tests.

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

(f) Data presented are the average of four tests.

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

Compound	Dose (μg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c) Summary: Positive								
Dimethyl sulfoxide		50	1,045	459	0.44	9.2	26.0	
Benzaldehyde	5	50	1,045	481	0.46	9.6	26.0	104.3
	16	50	1,045	512	0.49	10.2	26.0	110.9
	50	50	1,044	567	0.54	11.3	26.0	122.8
	160	50	1,034	689	0.67	13.8	26.0	150.0
Triethylenemelamine	0.015	50	1,044	1,781	1.71	35.6	26.0	387.0
+S9 (d) Summary: Weakly positive								
Dimethyl sulfoxide		50	1,048	431	0.41	8.6	26.0	
Benzaldehyde	160	50	1,049	469	0.45	9.4	26.0	109.3
	500	50	1,047	489	0.47	9.8	26.0	114.0
	1,600	50	1,050	566	0.54	11.3	26.0	131.4
Cyclophosphamide	1	50	1,049	1,165	1.11	23.3	26.0	270.9

(a) Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

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

−S9 (b) Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	+S9 (c) Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 14 hours					Harvest time: 14 hours				
Dimethyl sulfoxide					Dimethyl sulfoxide				
100	3	0.03	3.0	3.0	100	3	0.03	3.0	3.0
Benzaldehyde					Benzaldehyde				
50	100	3	0.03	3.0	160	100	5	0.05	5.0
160	100	3	0.03	3.0	500	100	3	0.03	3.0
500	100	3	0.03	2.0	1,600	100	6	0.06	6.0
Summary: Negative					Summary: Negative				
Triethylenemelamine					Cyclophosphamide				
0.15	100	34	0.34	25.0	15	100	57	0.57	32.0

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

TABLE H5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY BENZALDEHYDE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Feeding	1,150	24	3	3/2,053	0/1,871	2/1,885	5/5,809 (0.09%)
	0			0/2,039	3/1,877	0/1,740	3/5,656 (0.05%)
Injection	2,500	12	0	5/2,774	4/1,739	0/1,594	9/6,107 (0.15%)
	0			3/2,966	0/2,537	3/2,392	6/7,895 (0.08%)

(a) Study performed at University of Wisconsin--Madison. A detailed protocol of the sex-linked recessive lethal assay is presented by Woodruff et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were not significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft of NTP Technical Report No. 378 for the 2-year studies of benzaldehyde in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audit included review of:

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

Procedures and events for the exposure phase of the studies were documented adequately, with the exception that archival records needed to document part or all of the following were not at the Archives: room air change rate; room light cycle; type of cage, filter, rack, feeder, bedding, and detergents used; method of animal kill; and red-lined pathology tables for mice. Review of the available records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the preparation, analysis, and administration of doses to animals were complete and accurate. The review of body weight records showed that 48/48 recalulated mean values were correct and that the original records contained data for 4 weeks that had not been included in, but have since been added to, the Technical Report.

Data entries on necropsy forms were made appropriately for rats and mice. Each external mass recorded during the last few months of the life correlated with an observation recorded at necropsy, except for 17 in rats and 5 in mice. The date of death and disposition code recorded at necropsy for each unscheduled-death animal (118 rats and 112 mice) had matching entries among the inlife, animal-removal records. The condition code assigned at necropsy was consistent with gross observations and tissue accountability.

Individual animal identifiers (on ears and toes) were present and correct in the residual tissue bags for 43/51 rats and 56/56 mice examined. Review of the entire data trail for the eight rats with less than complete and correct identifiers indicated that the integrity of individual animal identity had been maintained. A total of 6 untrimmed potential lesions (1 involved the skin) was found in the wet

tissues of 51 rats examined, and 5 lesions (3 involved the forestomach) were found in the wet tissues of 56 mice examined. Histopathology that was performed on the forestomach of female mice subsequent to the audit identified additional diagnoses of hyperplasia and squamous papilloma; these data were incorporated into the Technical Report. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but three in rats and seven in mice. Blocks and slides were present and labeled correctly; corresponding tissue sections in blocks and on slides matched each other properly. All post-Pathology Working Group changes in diagnoses for rats had been incorporated into the final pathology tables. Rates for the incidence of neoplasms given in the Technical Report were the same as those in the final pathology tables at the Archives.

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