NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 343

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZYL ALCOHOL

(CAS NO. 100-51-6)

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 BENZYL ALCOHOL

(CAS NO. 100-51-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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June 1989

NTP TR 343

NIH Publication No. 89-2599

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

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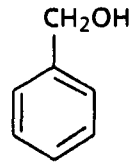

BENZYL ALCOHOL

CAS No. 100-51-6

C_7H_8O Molecular weight 108

Synonyms: benzenemethanol; phenylcarbinol; phenylmethanol; α-hydroxytoluene; benzenecarbinol; phenolcarbinol; α-toluenol

ABSTRACT

Toxicology and carcinogenesis studies of technical-grade benzyl alcohol (99% pure), a textile dye additive, solvent, and food flavoring agent, were conducted by administering the chemical by gavage in corn oil vehicle to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 days, 13 weeks, or 2 years.

Short-Term Studies: In 16-day studies, all five male and five female rats and mice dosed with 2,000 mg/kg benzyl alcohol died. Two of five male and 3/5 female rats and 1/5 male and 2/5 female mice dosed with 1,000 mg/kg died. Rats and mice of each sex in the two highest dose groups were lethargic after dosing. Other toxic responses to benzyl alcohol in these dose groups included blood around the mouth and nose, subcutaneous hemorrhages, and blood in the urinary and gastrointestinal tracts of rats and blood in the urinary bladder of mice. Animals administered lower doses of benzyl alcohol (125, 250, or 500 mg/kg) had no compound-related histologic lesions.

Doses selected for the 13-week studies were 0, 50, 100, 200, 400, and 800 mg/kg for rats and mice. Eight of 10 male rats dosed with 800 mg/kg died during weeks 7 and 8; four of these deaths were described as gavage related. Rats dosed with 800 mg/kg exhibited clinical signs indicative of neurotoxicity including staggering, respiratory difficulty, and lethargy. Hemorrhages occurred around the mouth and nose, and there were histologic lesions in the brain, thymus, skeletal muscle, and kidney. In mice, deaths were scattered among all dose levels, but none occurred in vehicle controls. Four male and six female mice died after being dosed; all deaths but one were described as gavage related. Staggering after dosing also occurred during the first 2 weeks of the studies in mice dosed with 800 mg/kg. Some of the deaths in the rats and mice may have been caused by a combination of the gavage procedure and chemical toxicity, since there was evidence that benzyl alcohol induced neurotoxic effects. There were reductions in relative weight gain in male rats dosed with 800 mg/kg benzyl alcohol, in female rats dosed with 200 mg/kg or more, in male mice dosed with 400 or 800 mg/kg, and in female mice dosed with 200 mg/kg or more. No notable changes in body weight gain or compound-related histopathologic lesions were observed in rats or mice from the lower dose groups. Based on mortality, reduction in relative body weight gain, and the histopathologic lesions, doses selected for 2-year studies in rats were 0, 200, and 400 mg/kg. Doses selected for 2-year studies in mice were 0, 100, and 200 mg/kg, based on mortality and depression in relative body weight gain.

Body Weight and Survival in the Two-Year Studies: Fifty animals of each species and sex were administered benzyl alcohol in corn oil by gavage 5 days per week for 103 weeks. Administration of benzyl alcohol did not affect survival in male rats (final survival rates: vehicle control, 28/50; low dose, 27/50; high dose, 24/50) but reduced survival of dosed female rats by half (36/50; 18/50; 17/50). Many of the early deaths were considered related to the gavage procedure. Survival in mice was not

affected by benzyl alcohol administration (male: 34/50; 33/50; 35/50; female: 26/50; 32/50; 36/50). No effect of benzyl alcohol on body weight gain in rats or mice was observed. In the third month of the studies, clinical signs of sialodacryoadenitis virus infection were observed in rats. A positive serologic reaction for rat coronavirus was observed in sentinel animals at 6 months and again at 18 months.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: No apparent compound-related nonneoplastic responses were observed. Dose-related negative trends in the incidences of anterior pituitary gland neoplasms were seen in female rats (vehicle control, 29/50; low dose, 17/47; high dose, 9/49) and of harderian gland adenomas in male mice (8/50; 3/50; 2/50). Adenomas of the adrenal cortex occurred at an increased incidence in high dose male mice (0/48; 0/44; 3/48), but this slight increase was not considered to be related to chemical exposure.

Genetic Toxicology: Benzyl alcohol was not mutagenic when tested by the preincubation protocol in the presence or absence of exogenous metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537. In the mouse L5178Y/TK$^{+/-}$ lymphoma assay, benzyl alcohol induced an increase in trifluorothymidine (Tft)-resistant cells in the absence, but not in the presence, of S9; the effect was associated with toxicity. In cytogenetic assays with Chinese hamster ovary (CHO) cells, treatment with benzyl alcohol produced an increase in sister chromatid exchanges (SCEs) which was judged to be equivocal both with and without S9; a significant increase in chromosomal aberrations was observed after exposure to benzyl alcohol in the presence, but not the absence, of S9.

Audit: The data, documents, and pathology materials from the 2-year studies of benzyl alcohol have been audited. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg. Survival in both dose groups of female rats was 50% that of vehicle controls, primarily due to an increased number of gavage-related deaths. There was *no evidence of carcinogenic activity* of benzyl alcohol for male or female B6C3F$_1$ mice dosed with 100 or 200 mg/kg for 2 years.

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

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF BENZYL ALCOHOL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 200, or 400 mg/kg benzyl alcohol in corn oil, 5 d/wk	0, 200, or 400 mg/kg benzyl alcohol in corn oil, 5 d/wk	0, 100, or 200 mg/kg benzyl alcohol in corn oil, 5 d/wk	0, 100, or 200 mg/kg benzyl alcohol in corn oil, 5 d/wk
Body weights in the 2-year study			
Comparable among all groups	Comparable among all groups	Comparable among all groups	Comparable among all groups
Survival rates in the 2-year study			
28/50; 27/50; 24/50	36/50; 18/50; 17/50	34/50; 33/50; 35/50	26/50; 32/50; 36/50
Nonneoplastic effects			
None	None	None	None
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence
Genetic toxicology			
S. typhimurium (gene mutation)	Mouse L5178Y/TK$^{+/-}$ (Tft resistance)	CHO Cells in Vitro	
		SCE	Aberration
Negative with and without S9	Negative without S9; positive with S9	Equivocal with and without S9	Positive without S9; negative with S9

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 Benzyl Alcohol is based on the 13-week studies that began in March 1980 and ended in June 1980 and on the 2-year studies that began in January 1981 and ended in March 1983 at Microbiological Associates (Bethesda, Maryland).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on benzyl alcohol on November 6, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZYL ALCOHOL

On November 6, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of benzyl alcohol received peer 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, North Carolina.

Dr. M.P. Dieter, NTP, introduced the toxicology and carcinogenesis studies by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenic activity for male or female rats or for male or female mice).

Dr. Ashby, a principal reviewer, agreed with the conclusions. He noted the positive genetic toxicity findings reported for gene mutation in mouse lymphoma cells and for chromosomal aberrations in Chinese hamster ovary (CHO) cells. However, Dr. Ashby stated that benzyl alcohol was a classic example of a nongenotoxic noncarcinogen that appears to be genotoxic in vitro only in the presence of toxicity. He said that the discussion should be revised to reflect this [see page 45].

Dr. Hughes, a second principal reviewer, agreed with the conclusions. He commented on aspects of the conduct of the studies, specifically the greater incidence of accidental gavage deaths in dosed rats compared with that in vehicle controls and the dosing error that occurred in male and female mice during week 80. He wondered whether either might have compromised the integrity of the studies. Dr. Dieter replied that the gavage accidents appeared to be due to a combination of faulty gavage procedure and the anesthetic properties of benzyl alcohol. He felt that although the increased mortality somewhat reduced the sensitivity, there was no question that the results were negative for rats and that the misdosing with α-methylbenzyl alcohol did not affect the outcome in mice. Dr. Haseman added that there was no hint of increased tumor incidences in dosed rats.

Dr. Chinchilli, a third principal reviewer, was unable to attend the meeting. Dr. L. Hart, NIEHS, read his review, in which Dr. Chinchilli agreed with the proposed conclusions.

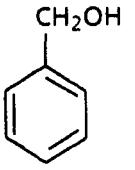
In other discussions, Dr. Mirer and Dr. Ashby noted the similarities in chemical structure and metabolic pathways between benzyl alcohol and benzyl acetate and asked for enhanced discussion of this comparison. Dr. Perera asked for clarification of a change in interpretation of NTP genetic toxicity results originally reported in the conclusions as "weakly positive" for sister chromatid exchanges (SCEs) in CHO cells. A revision of this section that was distributed to the Panel termed the findings for SCEs "equivocal." She also asked why a paragraph discussing the genotoxicity of metabolites of benzyl alcohol had been deleted in the revised section. Dr. J. Bishop, NIEHS, responded that the overall conclusion for SCEs has always been equivocal. Both with and without metabolic activation, results for one of the two trials in each of these situations were weakly positive because a significant increase was observed only at the highest dose. The original Discussion paragraph on the genotoxicity of benzyl alcohol described the results of cytogenetic tests as demonstrating induction of both SCEs and chromosomal aberrations. Dr. Bishop said that it should have noted that the SCE response was judged equivocal, as correctly stated in the Abstract and Introduction sections. Dr. Bishop said that information on the genotoxicity of the metabolites of benzyl alcohol was already present in the Introduction. However, paragraphs would be added to the Discussion describing the genotoxicity of α-methylbenzyl alcohol and benzyl acetate [see page 45].

Dr. Ashby moved that the Technical Report on benzyl alcohol be accepted with revisions as discussed and with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Hughes seconded the motion, which was approved unanimously by the Panel members.

I. INTRODUCTION

Physical Properties and Purity
Production, Use, and Exposure
Acute Toxicity
Absorption, Distribution, and Metabolism
Genetic Toxicity
Carcinogenicity
Study Rationale

I. INTRODUCTION



BENZYL ALCOHOL

CAS No. 100-51-6

C_7H_8O Molecular weight 108

Synonyms: benzenemethanol; phenylcarbinol; phenylmethanol; α-hydroxytoluene; benzenecarbinol; phenolcarbinol; α-toluenol

Physical Properties and Purity

Benzyl alcohol is a colorless liquid with a faint aromatic odor and a sharp, burning taste. The chemical has a freezing point of −15.19° C, a boiling point of 204.7° C, a specific gravity of 1.0435, and a refractive index of 1.54035; it has a vapor pressure of 1 mm mercury at 58° C, is sparingly soluble in water (1 g/25 g), and is freely soluble in 50% alcohol (Merck, 1983). It is miscible with alcohol, ether, and chloroform.

Production, Use, and Exposure

Benzyl alcohol was originally produced by the Cannizzaro reaction between benzaldehyde and potassium hydroxide but is now commercially produced by the action of sodium or potassium carbonate on benzyl chloride (Merck, 1983).

Available production data for benzyl alcohol were based on the amount of benzyl chloride converted to benzyl alcohol, using a conversion factor of 1.5 units (CEH, 1983). Benzyl alcohol production was estimated to be 7.5 million lb in 1978, 1.5 million lb in 1981, and 3.4 million lb in 1986. Approximately 834,000 lb of benzyl alcohol was imported in 1981 (USITC, 1982), 1,700,000 lb in 1982 (USITC, 1983), and 1,800,000 lb in 1983 (USITC, 1984). Benzyl alcohol occurs naturally in plant oils (Fenaroli, 1971; Opdyke, 1973), is a known human metabolite of styrene (Milvy and Garro, 1976), and is a photodecomposition product of the insecticide bioresethrin (Ueda et al., 1974). Benzyl alcohol has been detected in industrial effluents in the United States (Shackelford and Keith, 1976; CEH, 1977). Estimates of human exposure to benzyl alcohol in cosmetics, food, and drugs range up to 1.9×10^8 g (400,000 pounds) per year by routes that include dermal, oral, and inhalation.

The primary use of benzyl alcohol is as a co-additive in the textile dyeing industry (Kirk-Othmer, 1978). The chemical also is used in the manufacture of other benzyl compounds and as a solvent for gelatin, casein, cellulose acetate, and shellac. It is an ingredient in perfumes and food flavorings, mostly in the form of its aliphatic esters. It is used as an embedding material in microscopy and as a bacteriostat in pharmaceuticals.

Acute Toxicity

Benzyl alcohol is an irritant to skin and eyes; mild skin irritation at 10 mg for 24 hours and severe irritation at 750 µg in the eyes of rabbits have been reported (NIOSH, 1983).

The oral LD_{50} values in rats and mice range between 1,230 and 1,580 mg/kg, the intravenous LD_{50} value is 64 mg/kg in rats and 324 mg/kg in mice, the subcutaneous LD_{50} value is 1,700 mg/kg, and the intraperitoneal LD_{50} value is 400 mg/kg in rats; the inhalation LC_{Lo} value in rats was reported to be 1,000 ppm for 8 hours (NIOSH, 1983).

Absorption, Distribution, and Metabolism

Benzyl alcohol is readily absorbed from the alimentary tract and rapidly oxidized to benzoic

acid, which is conjugated with glycine and excreted as hippuric acid in the urine; higher doses result in excretion of the benzyl alcohol conjugated with glucuronide (Williams, 1959). Benzyl alcohol was shown to be an intermediate product in the metabolic pathway of benzyl acetate (Chidgey et al., 1986), for which the subsequent metabolism was identical to that of benzyl alcohol (Clapp and Young, 1970; Abdo et al., 1985).

Genetic Toxicity

Results of assays for mutagenic activity of benzyl alcohol in bacteria were uniformly negative. Benzyl alcohol did not induce growth inhibition due to DNA damage in *Escherichia coli* (Fluck et al., 1976) or *Bacillus subtilis* (Oda et al., 1978), nor was it mutagenic in any of several strains of *Salmonella typhimurium* when tested in the presence or absence of exogenous metabolic activation (Milvy and Garro, 1976; Florin et al., 1980; Wiessler et al., 1983). Likewise, NTP studies with benzyl alcohol in a preincubation protocol with *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9, showed no increase in revertant colonies (Mortelmans et al., 1986; Table E1).

In an NTP mouse L5178Y/TK$^{+/-}$ lymphoma assay, benzyl alcohol induced trifluorothymidine resistance in the absence, but not the presence, of Aroclor 1254-induced male F344 rat liver S9 (Table E2).

Exposure of human cell cultures to an unspecified amount of benzyl alcohol did not result in DNA single-strand breaks or chromosomal aberrations (Waters et al., 1982). In NTP cytogenetic tests, treatment of Chinese hamster ovary (CHO) cells with benzyl alcohol, both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9, produced an equivocal increase in sister chromatid exchanges (SCEs); in both cases, a weakly positive response was observed at the highest dose tested in one of two trials (Table E3). Chromosomal aberrations were observed in CHO cells after exposure at 4,000 µg/ml benzyl alcohol in the presence of S9. In the absence of S9, three of four trials gave a negative response; benzyl alcohol was concluded to be negative in this assay in the absence of S9 (Table E4).

Several structural analogs and metabolites of benzyl alcohol have been identified, and the genotoxicity data suggest that, as with benzyl alcohol, these related compounds are probably not strong mutagens, but evidence of clastogenicity has been reported. The metabolites of benzyl alcohol for which such data are available include benzaldehyde, benzoic acid, and hippuric acid. Results of bacterial gene mutation assays are negative for all three compounds (Kikuchi et al., 1977; Simmon and Kauhanen, 1978; Gocke et al., 1981; Haworth et al., 1983). In addition, benzoic acid did not induce mitotic recombination in yeast (Simmon and Kauhanen, 1978), chromosomal aberrations in human peripheral blood lymphocytes (Zhurkov, 1975), or SCEs in human lymphoblastocytes (Tohda et al., 1980). A 50 mM dose of benzaldehyde was reported to induce chromosomal aberrations in cultured CHO cells following a 24-hour exposure period and a 24-hour recovery period (Kasamaki et al., 1982), but this response was not observed in NTP cytogenetic assays with CHO cells exposed to benzaldehyde at doses of 500 µg/ml without S9 and 1,600 µg/ml with S9 (Galloway et al., 1987). Positive responses were observed, however, in the SCE test with and without S9 (Galloway et al., 1987) and in the mouse lymphoma L5178Y/TK$^{+/-}$ assay.

Limited mutagenicity data are available on the structural analogs 4-chlorobenzyl alcohol, 4-methylbenzyl alcohol, α-methylbenzyl alcohol, benzene-ethanol, and toluene. Like the metabolites, all are negative in bacterial gene mutation assays (Momii et al., 1979; Florin et al., 1980; Haworth et al., 1983; Zeiger et al., 1987; NTP unpublished data). Results from NTP mouse lymphoma forward mutation assays were positive without S9 for α-methylbenzyl alcohol and equivocal for toluene. In NTP cytogenetic assays with cultured CHO cells, neither α-methylbenzyl alcohol nor toluene induced SCEs; however, α-methylbenzyl alcohol induced chromosomal aberrations in the presence of S9 (NTP, in preparation).

Carcinogenicity

No carcinogenicity studies of benzyl alcohol have been reported, but benzyl acetate, which is metabolized to benzyl alcohol in vivo, was reported to induce acinar cell adenomas of the exocrine pancreas in male F344/N rats and hepatocellular adenomas and squamous cell neoplasms of the forestomach in male and female $B6C3F_1$ mice (Abdo et al., 1985; NTP, 1986).

Study Rationale

Benzyl alcohol was nominated by the National Cancer Institute for toxicity and carcinogenicity evaluation as a representative from the class of aromatic alcohols. Although the principal use of benzyl alcohol is in the dye industry, the aliphatic esters of this chemical are used as flavoring agents in food, and metabolic de-esterification would yield benzyl alcohol, resulting in widespread human exposure in food products. Human exposure is also through pharmaceutical products that incorporate benzyl alcohol. Benzyl alcohol is volatile, which necessitated gavage administration for the 2-year studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BENZYL ALCOHOL

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF BENZYL ALCOHOL

Benzyl alcohol, NF grade, was obtained in one lot (lot no. 4T 215P1) from Stauffer Chemical Co. (Westport, Connecticut). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). MRI reports on analyses performed in support of the benzyl alcohol studies are on file at NIEHS.

The study chemical was identified as benzyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (Figures 1 and 2) were consistent with those expected for the structure of benzyl alcohol and with spectra in the literature (Sadtler Standard Spectra). The study material had a boiling point at 734 mm mercury of 204.2° C and a density at 23° C of 1.04648 g/ml. The purity of benzyl alcohol was determined by elemental analysis, Karl Fischer water analysis, titration for aldehyde impurities, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: *n*-hexane:acetone (85:15) and ethyl acetate. Gas chromatographic analysis was performed with flame ionization detection and a 10% Carbowax 20M TPA column (system 1) or a 20% SP2100/0.1% Carbowax 1500 column (system 2). Aldehyde impurities were detected by reacting the benzyl alcohol study material with hydroxylamine hydrochloride to liberate hydrochloric acid, which was then titrated with sodium hydroxide. The cumulative data indicated that lot no. 4T 215P1 was approximately 99% pure. Results of the elemental analyses agreed with the theoretical values. Water content was 0.078%. Aldehyde content (as benzaldehyde) was less than 0.1%. Only the major component was detected by thin-layer chromatography with both solvent systems. Gas chromatography with system 1 indicated four impurities with peak areas totaling 0.25% relative to the major peak area. Gas chromatography with system 2 indicated a single impurity with a relative area of 0.01%. The density, boiling point, and aldehyde content conformed to NF standards.

Stability studies performed by gas chromatography with the same column as that described above for system 1 indicated that benzyl alcohol was stable in the dark at temperatures up to 60° C for 2 weeks. Benzyl alcohol was stored at 4° C until March 1982 and then at room temperature during the toxicity and carcinogenicity studies. Results of periodic analysis of the bulk chemical by infrared spectroscopy and gas chromatography indicated that no notable degradation occurred during the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dose mixtures were prepared by mixing the appropriate amounts of benzyl alcohol and corn oil (Table 1). The stability of benzyl alcohol in corn oil (80 mg/ml) was determined by methanol extraction and gas chromatography with the same column as that described for system 2. The chemical in corn oil was found to be stable for up

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF BENZYL ALCOHOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation Appropriate weight of chemical mixed with corn oil in volumetric flasks, stoppered, and thoroughly mixed	Same as 16-d studies	Same as 16-d studies
Maximum Storage Time 8 d	15 d	Rats--3 wk; mice--2 wk
Storage Conditions Room temperature	Room temperature	Room temperature

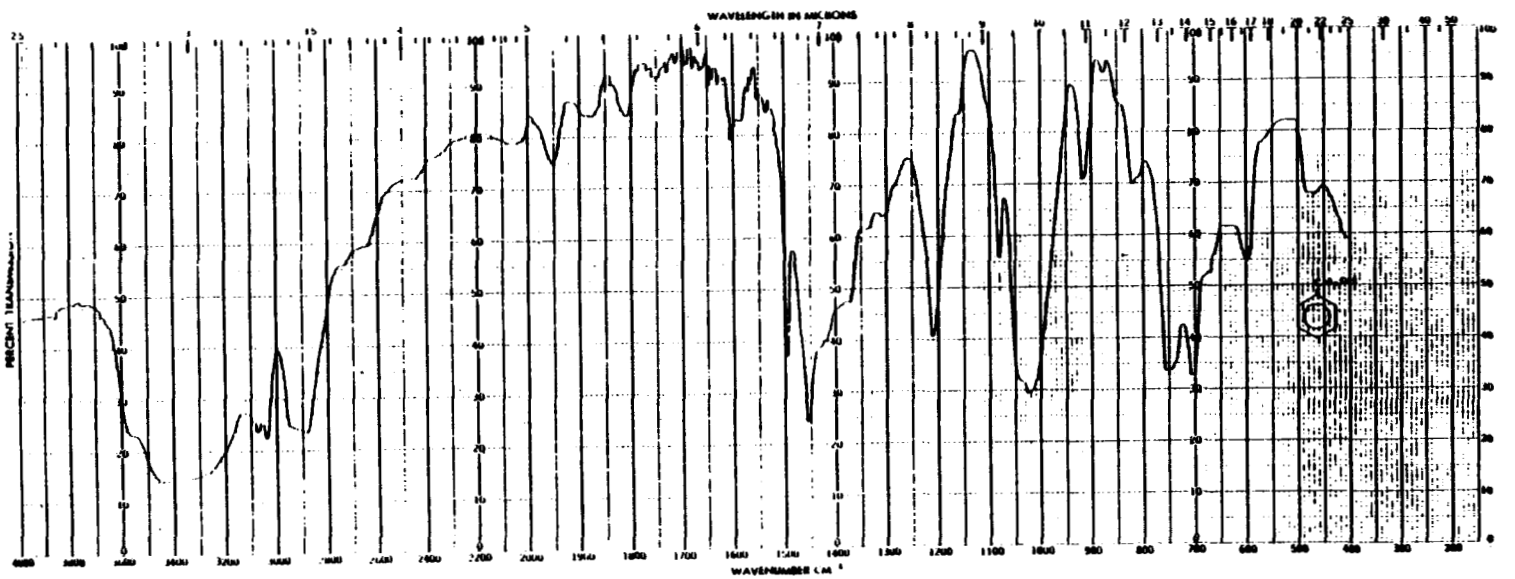


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF BENZYL ALCOHOL (LOT NO. 4T 215P1)

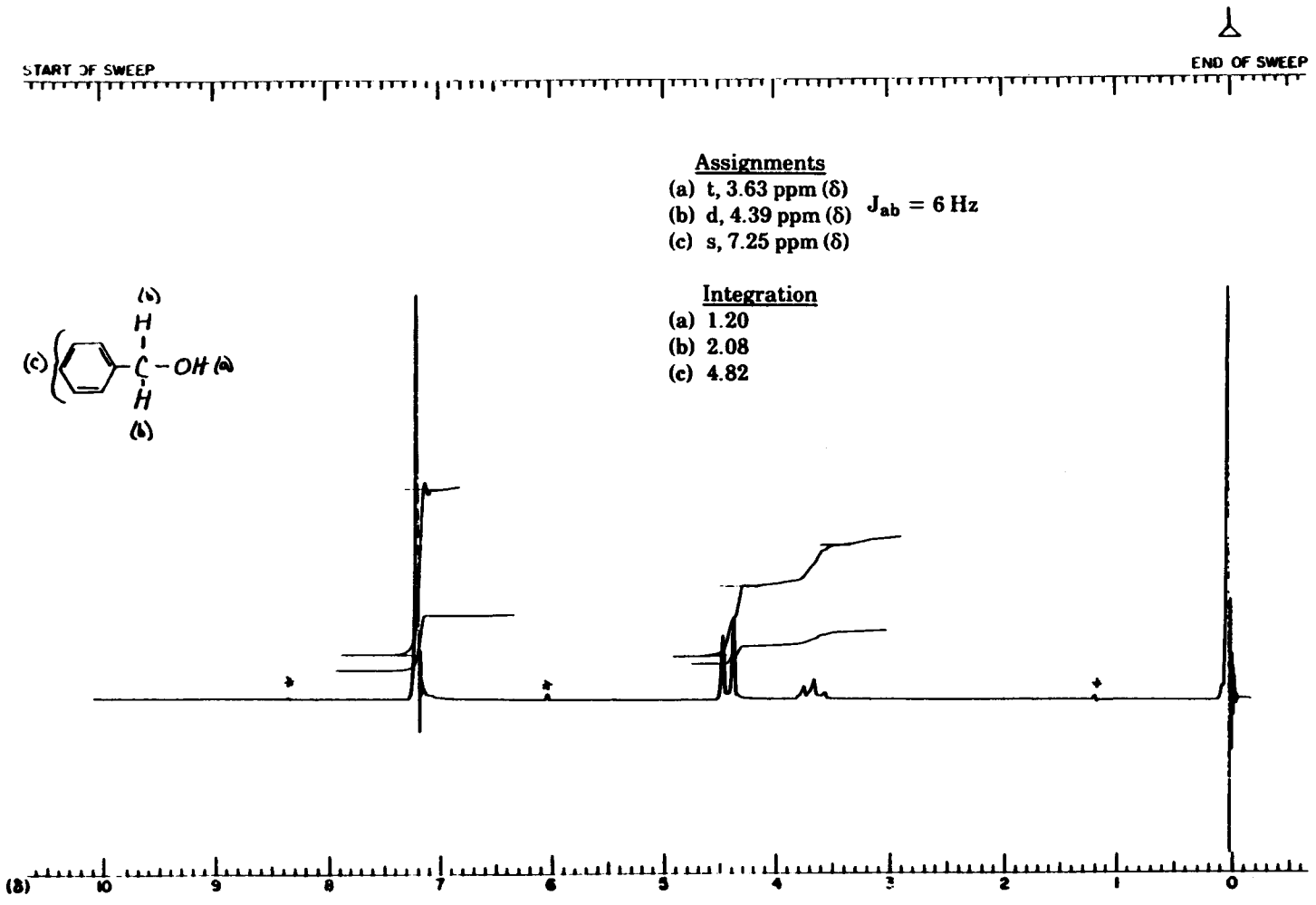


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BENZYL ALCOHOL (LOT NO. 4T 215P1)

to 7 days in the dark at room temperature. Results obtained by the study laboratory showed that benzyl alcohol in corn oil at 5 or 80 mg/ml was stable for at least 14 days at room temperature. During the 13-week studies, benzyl alcohol/corn oil mixtures were stored at room temperature for no longer than 15 days. During the 2-year studies, the mixtures were stored at room temperature until February 1983 and then at 5° C for no longer than 3 weeks for rats and 2 weeks for mice.

Periodic analysis of the benzyl alcohol/corn oil dose mixtures was conducted at the study and analytical chemistry laboratories by extraction of benzyl alcohol with methanol followed by gas chromatographic analysis with system 2 and heptyl alcohol as an internal standard. Dose mixtures were analyzed once during the 13-week studies, and results ranged from 101% to 108% of the target values (Table 2). During the 2-year studies, the dose preparations were analyzed at approximately 8-week intervals. Throughout the benzyl alcohol studies, the mixtures were formulated within ±10% of the target concentrations 100% (54/54) of the time (Table 3). Results of periodic referee analysis performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Table 4).

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZYL ALCOHOL (a)

Concentration of Benzyl Alcohol in Corn Oil (mg/ml)		Determined as a Percent of Target
Target	Determined (b)	
5.0	5.2	105
10.0	10.6	106
20.0	21.2	106
40.0	40.8	102
80.0	86.4	108
160.0	161	101

(a) Date mixed: 3/7/80; dates analyzed: 4/14/80-4/17/80
(b) Results of duplicate analysis

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL

Date Mixed	Concentration of Benzyl Alcohol in Corn Oil for Target Concentration (mg/ml) (a)			
	10	20	40	80
12/31/80	9.7	20.1		
01/14/81			39.4	76.0
02/26/81	9.4	19.5	39.8	73.9
04/23/81	10.1	20.1	41.2	77.6
06/18/81	10.2	20.2	42.1	80.2
08/13/81	9.7	19.0	38.9	77.8
10/08/81	9.0	18.3	40.0	83.1
12/03/81	10.1	21.4	40.2	78.7
01/28/82	9.7	20.4	42.4	84.7
03/25/82	9.6	20.0	41.6	86.5
05/20/82	10.7	21.0	41.2	82.4
07/15/82	10.3	20.3	40.7	81.7
09/09/82	9.8	19.9	41.5	85.4
11/04/82	9.4	20.5	39.3	82.9
12/30/82			39.8	86.5
Mean (mg/ml)	9.8	20.1	40.6	81.2
Standard deviation	0.45	0.80	1.10	3.98
Coefficient of variation (percent)	4.6	4.0	2.7	4.9
Range (mg/ml)	9.0-10.7	18.4-21.4	38.9-42.4	73.9-86.5
Number of samples	13	13	14	14

(a) Results of duplicate analysis except for single analysis for mix dates 12/31/80-4/23/81

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
02/26/81	40	(c) 39.8	38.9
08/13/81	20	19.0	20.0
03/25/82	80	86.5	79.9
11/04/82	10	9.4	10.0

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

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Rats and mice were held for 19 days before the studies began. The animals were 8 weeks old when placed on study.

Groups of five rats and mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg benzyl alcohol in corn oil by gavage on 12 days over a 16-day period. Animals were housed five per cage. Water and feed were available ad libitum.

Rats and mice were observed two times per day and weighed once per week. A necropsy was performed on all animals. Tissues and groups examined are listed in Table 5.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZYL ALCOHOL

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		
0, 125, 250, 500, 1,000, or 2,000 mg/kg benzyl alcohol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	0, 50, 100, 200, 400, or 800 mg/kg benzyl alcohol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 200, or 400 mg/kg benzyl alcohol in corn oil by gavage; mice--0, 100, or 200 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
Rats--12/4/79; mice--12/3/79	3/10/80	Rats--3/30/81; mice--1/5/81
Date of Last Dose		
12/18/79	6/6/80	Rats--3/18/83; mice--12/23/82
Duration of Dosing		
5 d/wk for 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed individually initially and at the end of the studies; weighed by group at other times 1 × wk	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and then 1 × mo
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams performed on 3 male and 2 female rats in the 500 mg/kg groups, 3 female mice in the 1,000 mg/kg group, and 4 male mice in the 500 mg/kg group	Necropsy performed on all animals; histologic exams performed on all vehicle controls and animals in the 800 mg/kg groups. Brains were examined from rats and mice in the 400 mg/kg groups and from all mice dying before the end of the studies	Necropsy performed on all animals; histologic exams performed on all female rats and on vehicle control and high dose male rats and mice, male rats and mice that died before month 22, and male rats and mice with gross lesions; the following tissues were examined: adrenal glands, brain, cecum, clitoral or preputial gland, colon, costochondral junction, duodenum, esophagus, eyes, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, oral cavity, pancreas, parathyroids, pharynx, pituitary gland, rectum, salivary glands, sciatic nerve, scrotal sac/tunica vaginalis/seminal vesicles/prostate/epididymis/testes or ovaries/uterus, skin, spinal cord, spleen, sternebrae or vertebrae or femur including marrow, thigh muscle, thymus, thyroid gland, trachea, urinary bladder, and Zymbal gland; pituitary gland and testis examined for low dose male rats; adrenal glands, brain, kidney, liver, and lung examined for low dose male mice; brain, liver, spleen, and uterus examined for low dose female mice

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZYL ALCOHOL (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
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 (Portage, MI)	Charles River Breeding Laboratories (rats: Kingston, NY; mice: Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory Microbiological Associates	Microbiological Associates	Microbiological Associates
Method of Animal Identification Ear punch	Ear punch	Ear tag
Time Held Before Study 19 d	Rats--15 d; mice--16 d	Rats--26 d; mice--19 d
Age When Placed on Study 8 wk	Rats--7-8 wk; mice--7-9 wk	8-9 wk
Age When Killed 10 wk	Rats--20-21 wk; mice--20-22 wk	Rats--113 wk; mice--113-114 wk
Necropsy Dates Rats--12/20/79; mice--12/19/79	6/9/80-6/13/80	Rats--3/28/83-3/30/83; mice--1/3/83-1/6/83
Method of Animal Distribution Animals distributed to weight classes and assigned to cages according to a table of random numbers, and cages assigned to groups according to a table of random numbers	Same as 16-d studies	Same as 16-d studies
Feed Purina Lab Block (Chesapeake Feed Co., Beltsville, MD); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding Hardwood chips (P.J. Murphy Forest Products Corp., 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	Automatic watering system (Lab Products, Inc., Rochelle Park, NJ); available ad libitum
Cages Polycarbonate (Lab Products,Inc., Rochelle Park, NJ, or Hazleton Systems, Aberdeen, MD)	Same as 16-d studies	Same as 16-d studies
Cage Filters Spun-bonded polyester (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BENZYL ALCOHOL (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--65°-77° F; hum--35%-60%; fluorescent light 12 h/d; 10-15 room air changes/h	Temp--68°-81° F; hum--30%-90%; fluorescent light 12 h/d; 10-15 room air changes/h	Temp--66°-88° F; hum--20%-80%; fluorescent light 12 h/d; 10-15 room air changes/h

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of benzyl alcohol and to determine the doses to be used in the 2-year studies.

Five- to six-week-old male and female F344/N rats and 5- to 7-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 15 days (rats) or 16 days (mice), distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and vehicle control groups according to a table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 50, 100, 200, 400, or 800 mg/kg benzyl alcohol in corn oil by gavage, 5 days per week for 13 weeks. Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Animals were observed two times per day; moribund animals were killed. Animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 200, or 400 mg/kg benzyl alcohol in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 100, or 200 mg/kg according to the same schedule.

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 Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for 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 4-5 weeks of age, and mice at 5-6 weeks. The rats were quarantined at the study facility for 26 days, and the mice for 19 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 8-9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

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

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at 1-3 loci of the 12 loci tested, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

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

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Cages were not rotated during the first 90 weeks of the studies. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 12 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or missing. 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 (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. 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. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

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

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or 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: Three statistical methods are used to analyze tumor incidence data: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends. For studies in which administration of the study compound has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals

killed at the end of the study, were then combined by the Mantel-Haenszel method (1959) to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

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

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

SIXTEEN-DAY STUDIES

All rats that received 2,000 mg/kg and 2/5 males and 3/5 females that received 1,000 mg/kg died before the end of the studies (Table 6). The final mean body weight of male rats that received 1,000 mg/kg was 18% lower than that of the vehicle controls. Lethargy was observed at the two highest doses; rough hair coats were observed in the 500 mg/kg and 1,000 mg/kg groups of males and the 250 mg/kg and 500 mg/kg groups of females. Rats at 1,000 or 2,000 mg/kg had blood around the mouth and nose, subcutaneous hemorrhages, and blood in the urinary and gastrointestinal tracts. On days 8 and 9, the dose mixtures administered to the 125 mg/kg groups were tenfold too high. No compound-related histopathologic effects were found in the rats at any of the dose levels.

THIRTEEN-WEEK STUDIES

Eight of 10 male rats dosed with 800 mg/kg benzyl alcohol and 1 in the 200 mg/kg group died after being dosed; 1 vehicle control female rat, 1 in the 400 mg/kg group, and 2 in the 800 mg/kg group died after being dosed (Table 7). Five of these deaths were described as being related to the gavage procedures. After dosing, rats of each sex in the 800 mg/kg group exhibited signs of neurotoxicity, including staggering, labored breathing, and lethargy. Blood around the nose and mouth was observed in 5/10 males after 8 weeks of chemical administration with 800 mg/kg benzyl alcohol. The final mean body weight of rats that received 800 mg/kg was 7% lower than that of the vehicle controls for males and 5% lower for females. Compound-related histopathologic effects observed at 800 mg/kg

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF BENZYL ALCOHOL

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	177 ± 6	212 ± 5	+35 ± 2	
125	5/5	179 ± 10	209 ± 7	+30 ± 4	99
250	5/5	188 ± 8	218 ± 8	+30 ± 2	103
500	5/5	180 ± 6	206 ± 7	+26 ± 2	97
1,000	(d) 3/5	187 ± 4	174 ± 13	−16 ± 8	82
2,000	(e) 0/5	217 ± 8	(f)	(f)	(f)
FEMALE					
0	5/5	141 ± 3	147 ± 3	+6 ± 4	
125	5/5	145 ± 1	150 ± 3	+5 ± 2	102
250	5/5	149 ± 4	146 ± 5	−3 ± 6	99
500	5/5	142 ± 6	147 ± 4	+5 ± 5	100
1,000	(g) 2/5	138 ± 4	140 ± 8	−7 ± 9	95
2,000	(h) 0/5	134 ± 5	(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: 4,4
(e) Day of death: all 1
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 2,3,11
(h) Day of death: 1,1,2,2,2

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZYL ALCOHOL

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	146 ± 2	311 ± 5	+165 ± 6	
50	10/10	146 ± 3	307 ± 13	+161 ± 14	99
100	10/10	149 ± 2	326 ± 10	+177 ± 10	105
200	9/10	147 ± 2	327 ± 12	+181 ± 13	105
400	10/10	143 ± 2	317 ± 5	+174 ± 6	102
800	(d) 2/10	151 ± 2	288 ± 4	+138 ± 1	93
FEMALE					
0	9/10	116 ± 1	190 ± 8	+73 ± 8	
50	10/10	115 ± 1	186 ± 2	+71 ± 2	98
100	10/10	113 ± 1	184 ± 3	+71 ± 3	97
200	10/10	114 ± 1	177 ± 3	+63 ± 3	93
400	9/10	114 ± 1	172 ± 2	+58 ± 2	91
800	(e) 8/10	114 ± 1	180 ± 4	+65 ± 4	95

(a) Number surviving/number initially in the group; all deaths except those in the high dose groups were judged to be accidental.
(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: 7,8,8,8,8,8,8,8; four of the deaths were judged to be gavage related.
(e) One death during week 10 judged to be related to the gavage procedures; one additional death occurred between final weighing and terminal kill.

but not at lower doses included necrosis of the dentate gyrus of the hippocampus in 9/9 males and 7/7 females; skeletal muscle necrosis in 5/10 males; thymic congestion, hemorrhage, and atrophy in 8/10 males; and nephrosis in the kidney of 6/9 males. The renal lesions were not chemical specific and were similar to those seen in age-related spontaneous renal disease, consisting of degeneration and regeneration of the tubular epithelium.

Dose Selection Rationale: Because of reductions in relative weight gain, deaths, and lesions of the brain, thymus, skeletal muscle, and kidney, doses selected for rats for the 2-year studies were 200 and 400 mg/kg benzyl alcohol, 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 male and female rats were generally comparable throughout the studies (Table 8 and Figure 3). No compound-related clinical signs were observed. In the third month of the studies in rats, swelling in the cervical region, pink eyes, and a red exudate around the eyes were observed in rats from the vehicle control and both dosed groups. The clinical signs are characteristic of sialodacryoadenitis. This was confirmed by positive titers to rat coronavirus in sentinel animals.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL

Weeks on Study	Vehicle Control		200 mg/kg			400 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
1	213	50	212	100	50	211	99	49
2	237	50	237	100	50	225	95	48
4	276	50	275	100	50	270	98	48
5	284	49	286	101	50	273	96	48
6	303	49	297	98	50	287	95	48
7	311	49	309	99	50	299	96	48
8	320	49	322	101	50	318	99	48
9	331	49	328	99	50	319	96	47
10	337	49	341	101	50	331	98	47
11	340	49	347	102	50	347	102	46
12	344	48	346	101	50	348	101	46
15	373	48	369	99	50	360	97	46
18	384	48	384	100	48	376	98	46
22	401	48	409	102	47	399	100	46
25	422	48	424	100	46	414	98	46
30	439	48	439	100	46	427	97	46
34	452	48	452	100	46	441	98	46
37	460	48	459	100	46	448	97	46
41	466	48	470	101	45	456	98	46
45	479	48	478	100	42	465	97	46
49	486	48	490	101	42	472	97	42
54	495	48	495	100	41	482	97	42
57	493	48	495	100	40	486	99	40
62	496	46	500	101	40	494	100	40
65	498	46	492	99	40	500	100	39
69	488	46	506	104	40	509	104	39
73-74	498	45	501	101	40	498	100	39
77	496	44	504	102	40	510	103	38
81	499	43	507	102	39	509	102	36
85	496	43	505	102	39	512	103	35
89	493	40	503	102	37	514	104	35
93	477	37	484	101	36	479	100	33
99	467	30	461	99	34	495	106	26
101	458	29	461	101	30	485	106	25
FEMALE								
1	150	50	145	97	49	149	99	50
2	162	50	160	99	49	161	99	50
4	176	50	177	101	49	175	99	50
5	179	50	182	102	49	177	99	50
6	182	50	183	101	49	177	97	50
7	188	50	191	102	49	185	98	50
8	192	50	194	101	49	193	101	50
9	194	50	195	101	49	192	99	50
10	198	50	198	100	48	197	99	50
11	199	50	203	102	48	202	102	50
12	199	50	203	102	48	203	102	50
14-15	214	50	214	100	48	214	100	50
18	223	50	227	102	45	225	101	47
22	237	50	241	102	45	236	100	46
25	238	50	243	102	41	245	103	42
30	247	50	252	102	41	253	102	41
34	255	50	258	101	41	258	101	41
38	262	50	272	104	40	267	102	41
41	264	50	270	102	40	266	101	40
45	271	50	273	101	37	275	101	40
49	269	50	281	104	37	276	103	35
54	284	50	287	101	32	284	100	34
57	287	50	290	101	30	289	101	31
62	301	50	301	100	30	301	100	30
65	310	50	308	99	30	312	101	30
69	323	50	310	96	29	322	100	30
73	323	50	321	99	28	322	100	30
77	333	49	303	91	28	332	100	30
81	337	49	336	100	26	336	100	30
85	340	48	334	98	25	336	99	29
89	345	46	340	98	23	339	98	28
93	346	45	335	97	23	336	97	27
99	350	42	329	94	22	339	97	24
101	355	39	344	97	20	340	96	21

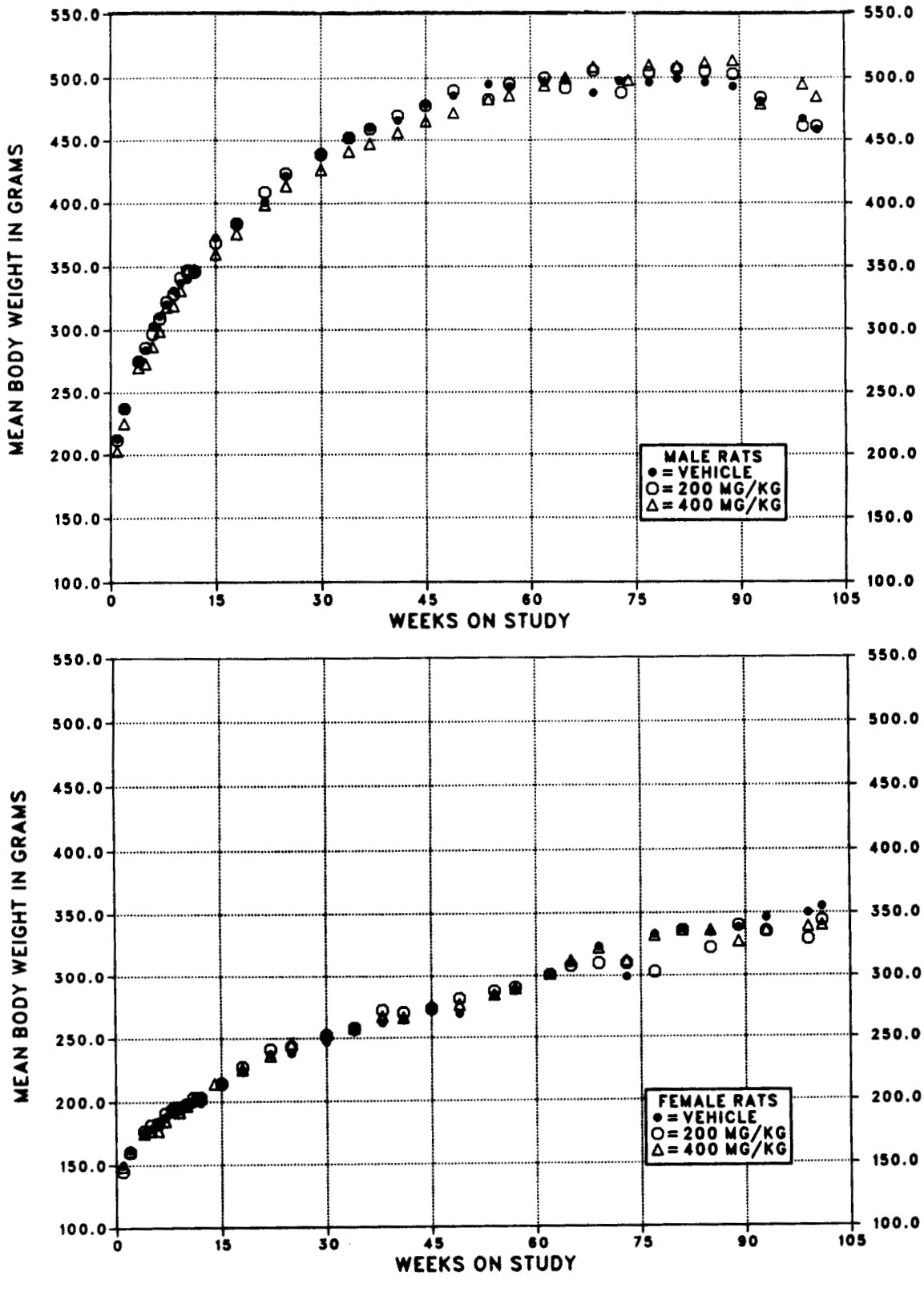


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED BENZYL ALCOHOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered benzyl alcohol at the doses used in these studies and for vehicle controls are shown in Table 9 and in the Kaplan and Meier curves in Figure 4. The survival of the low dose group of female rats was significantly lower than that of the vehicle controls between weeks 71 and 103; the survival of the high dose group was significantly lower than that of the vehicle controls after week 50.

Pathology and Statistical Analyses of Results

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.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL

	Vehicle Control	200 mg/kg	400 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	15	12
Accidentally killed (c)	4	8	14
Killed at termination	28	27	24
Survival P values (d)	0.516	0.727	0.589
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	16	20
Accidentally killed (e)	1	17	13
Killed at termination	35	17	17
Died during termination period	1	(f) 1	0
Survival P values (d)	0.012	0.059	0.013

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) All but one death were judged to be related to the gavage procedures.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(e) All deaths were judged to be related to the gavage procedures.
(f) Death after the beginning of the terminal-kill period was judged to be related to the gavage procedures; this animal is also included among those accidentally killed.

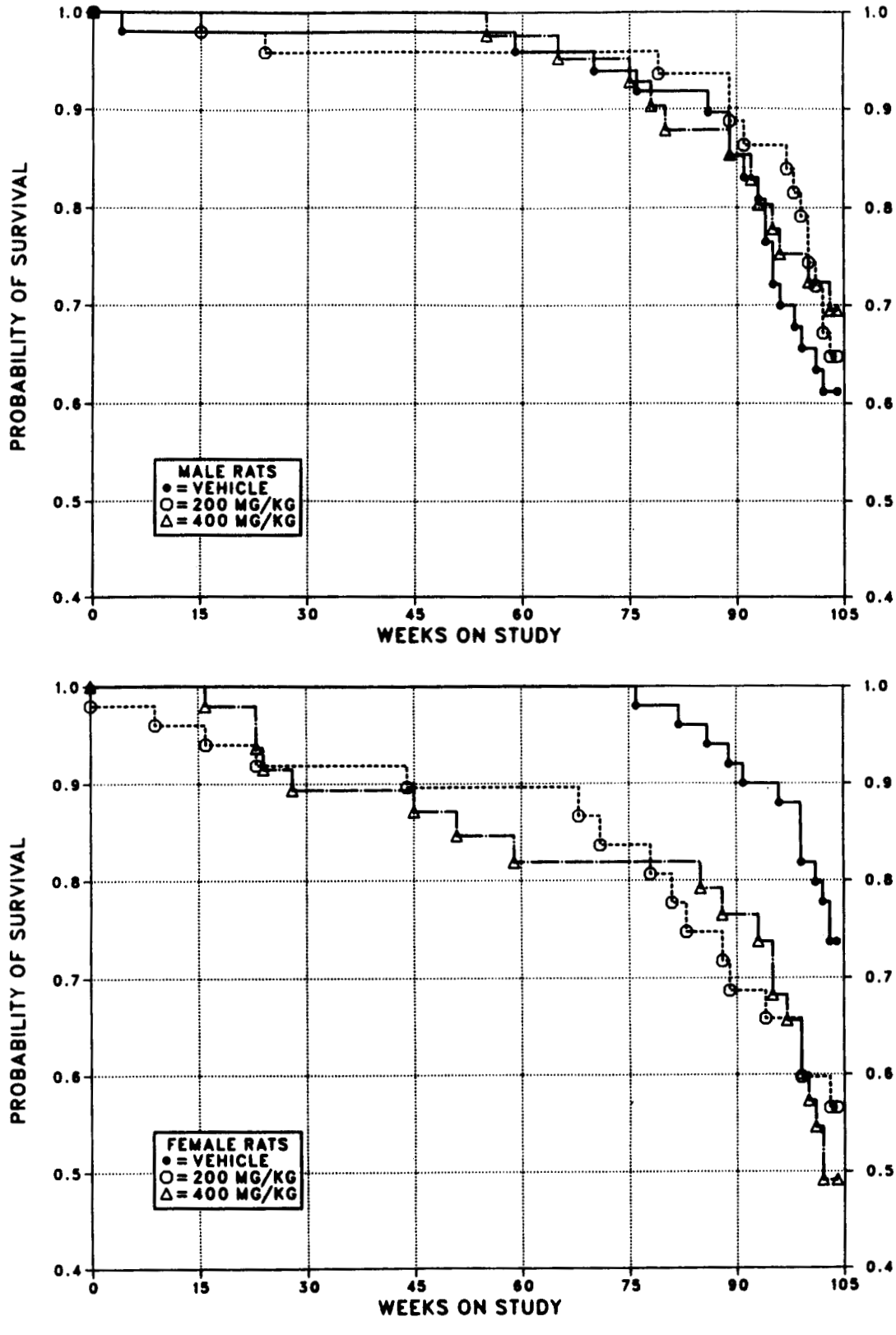


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED BENZYL ALCOHOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Eye: Cataracts and retinal atrophy were observed at increased incidences in high dose rats (cataracts--male: vehicle control, 2/50; low dose, 3/50; high dose, 23/50; female: 2/50; 2/50; 16/50; retinal atrophy--male: 1/50; 3/50; 24/50; female: 1/50; 3/50; 20/50). Records received after study termination indicated that the high dose animals were housed on the top two rows of cages except for the last 10 weeks of the studies, when cage rotation procedures were implemented. Thus, exposure to fluorescent light is the probable cause of the eye lesions.

Forestomach: Epithelial hyperplasia was seen in four high dose male rats. A squamous cell papilloma was seen in 1/19 low dose and 1/50 high dose male rats.

Lung: Hemorrhage and foreign material in the respiratory tract were seen at increased incidences in dosed rats that died before the terminal kill. In male rats, there were dose-related increases in acute inflammation in the nasal tract, hemorrhage in the larynx, and edema, hemorrhage, and foreign material in the lungs. The incidences of hemorrhage and foreign material in the lungs also were increased in dosed female rats.

Anterior Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female rats occurred with negative trends; the incidences in the high dose group were lower than those in the vehicle controls (Table 10).

TABLE 10. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Hyperplasia			
Overall Rates	5/50 (10%)	3/47 (6%)	6/49 (12%)
Adenoma			
Overall Rates	28/50 (56%)	17/47 (36%)	9/49 (18%)
Adjusted Rates	63.0%	64.0%	39.5%
Terminal Rates	20/36 (56%)	9/18 (50%)	5/17 (29%)
Week of First Observation	76	49	48
Life Table Tests	P=0.141N	P=0.310	P=0.109N
Incidental Tumor Tests	P=0.009N	P=0.429N	P=0.008N
Carcinoma			
Overall Rates	1/50 (2%)	0/47 (0%)	0/49 (0%)
Adenoma or Carcinoma (b)			
Overall Rates	29/50 (58%)	17/47 (36%)	9/49 (18%)
Adjusted Rates	63.8%	64.0%	39.5%
Terminal Rates	20/36 (56%)	9/18 (50%)	5/17 (29%)
Week of First Observation	76	49	48
Life Table Tests	P=0.113N	P=0.359	P=0.088N
Incidental Tumor Tests	P=0.004N	P=0.364N	P=0.004N

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table B3 (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 692/1,654 (42% ± 11%)

SIXTEEN-DAY STUDIES

The concentration of benzyl alcohol in dose mixtures administered to the 125 mg/kg groups on days 8 and 9 was tenfold too high; no adverse effects were observed. All mice that received 2,000 mg/kg and 1/5 males and 2/5 females that received 1,000 mg/kg benzyl alcohol died before the end of the studies (Table 11). Lethargy and rough hair coats were observed in the 500, 1,000, and 2,000 mg/kg groups of male mice and the 1,000 and 2,000 mg/kg groups of female mice. Mice at 1,000 and 2,000 mg/kg had blood in the urinary bladder at necropsy. No compound-related histopathologic effects were observed.

THIRTEEN-WEEK STUDIES

Deaths were observed in most dose groups, but none occurred in vehicle controls (Table 12). Four male and six female mice died after being dosed; all but one of the deaths were described as being related to the gavage procedures. The final mean body weights of female mice that received 400 or 800 mg/kg benzyl alcohol were 5% or 8% lower than that of the vehicle controls. High dose male and female mice exhibited staggering after dosing during the first and second weeks of the studies. No compound-related histopathologic effects were observed. Chronic interstitial pneumonia, consistent with a Sendai infection, was seen in all groups of mice.

Dose Selection Rationale: Because of reduction in relative weight gain at 400 and 800 mg/kg and the potential contribution of the anesthetic properties of benzyl alcohol to the gavage-related deaths, doses selected for mice for the 2-year studies were reduced to 100 and 200 mg/kg benzyl alcohol, administered by gavage in corn oil, 5 days per week.

TABLE 11. SURVIVAL OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF BENZYL ALCOHOL

Dose (mg/kg)	Survival (a)	
	Male	Female
0	5/5	5/5
125	(b) 4/5	(b) 4/5
250	5/5	5/5
500	5/5	5/5
1,000	(c) 4/5	(d) 3/5
2,000	(e) 0/5	(e) 0/5

(a) Number surviving/number initially in group. Equipment malfunction resulted in the final body weight data not being recorded; initial weights not reported by study laboratory.
(b) Death probably due to accidental overdose
(c) Day of death: 3
(d) Day of death: 8,11
(e) Day of death: all 1

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BENZYL ALCOHOL

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	27.8 ± 0.6	33.7 ± 0.5	+5.9 ± 0.7	
50	10/10	28.9 ± 0.6	33.2 ± 0.8	+4.3 ± 1.1	98.5
100	10/10	27.9 ± 0.3	34.1 ± 0.9	+6.2 ± 0.8	101.2
200	9/10	27.4 ± 0.5	33.8 ± 1.1	+6.4 ± 1.1	100.3
400	9/10	27.8 ± 0.9	32.1 ± 0.8	+4.3 ± 1.3	95.3
800	8/10	27.3 ± 0.6	32.0 ± 0.8	+4.9 ± 1.2	95.0
FEMALE					
0	10/10	21.0 ± 0.2	25.1 ± 0.4	+4.1 ± 0.4	
50	9/10	20.6 ± 0.3	25.4 ± 0.4	+4.8 ± 0.6	101.2
100	8/10	20.7 ± 0.3	25.9 ± 0.3	+5.2 ± 0.6	103.2
200	10/10	20.9 ± 0.2	23.9 ± 0.2	+3.0 ± 0.3	95.2
400	9/10	20.7 ± 0.3	23.8 ± 0.3	+3.0 ± 0.4	94.8
800	8/10	20.9 ± 0.3	23.0 ± 0.5	+2.1 ± 0.4	91.6

(a) Number surviving/number initially in group. One high dose female died during week 1; all other deaths were related to the gavage procedures.
(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

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control mice were generally comparable throughout the studies (Table 13 and Figure 5). No clinical signs were associated with chemical administration in male or female mice. During week 80 of the studies, the male and female mice were mistakenly dosed with 375 and 750 mg/kg α-methylbenzyl alcohol for 4 days, instead of with 100 and 200 mg/kg benzyl alcohol. No apparent adverse effect occurred.

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

Weeks on Study	Vehicle Control		100 mg/kg			200 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	23.8	50	23.9	100	50	23.7	100	50
1	25.2	50	25.3	100	50	25.4	101	50
2	26.4	50	26.8	102	50	26.3	100	50
3	27.4	50	27.9	102	50	27.3	100	50
4	28.8	50	29.2	101	50	28.6	99	50
5	29.1	50	29.9	103	50	29.1	100	50
6	29.6	50	30.8	104	50	30.6	103	50
7	31.5	50	32.1	102	50	31.8	101	50
8	30.8	50	31.9	104	50	31.3	102	48
9	31.9	50	32.4	102	50	30.8	97	48
10	33.0	49	33.3	101	50	32.5	98	48
11	34.1	49	34.4	101	50	33.3	98	48
12	34.1	49	34.2	100	50	33.7	99	48
14	34.9	49	35.2	101	50	34.5	99	48
19	36.6	48	37.1	101	50	35.9	98	48
23	38.5	47	39.5	103	50	39.8	103	48
27	39.9	47	40.5	102	49	41.8	105	48
32	41.8	47	42.6	102	49	43.4	104	48
34	41.9	47	42.9	102	49	42.9	102	48
38	41.9	47	43.5	104	48	42.6	102	48
42	42.5	46	43.6	103	48	42.5	100	48
46	42.6	46	43.7	103	48	42.8	100	47
50	42.6	45	43.5	102	48	41.8	98	47
54	43.1	43	43.9	102	47	43.3	100	47
58	45.1	42	45.8	102	47	43.8	97	46
62	45.0	41	46.6	104	47	45.9	102	45
66	45.1	41	46.9	104	46	46.0	102	44
70	44.5	40	45.7	103	44	45.2	102	43
74	44.9	40	46.6	104	43	47.6	106	42
79	45.9	39	47.0	102	41	44.6	97	42
82	45.1	39	46.1	102	41	45.4	101	42
86	43.9	38	44.3	101	39	44.8	102	41
94	42.0	38	43.6	104	35	44.0	105	40
98	42.7	38	43.0	101	33	43.7	102	35
102	42.5	35	43.2	102	33	42.4	100	35
FEMALE								
0	19.2	50	19.1	99	50	19.2	100	50
1	19.4	50	19.5	101	50	19.6	101	50
2	20.4	50	20.4	100	50	20.4	100	50
3	21.9	50	21.4	98	49	21.3	97	50
4	22.1	49	22.2	100	48	22.1	100	48
5	23.3	47	22.8	98	48	22.6	97	48
6	23.7	47	23.6	100	48	23.1	97	48
7	24.4	47	24.2	99	48	24.1	99	48
8	24.1	47	24.1	100	48	24.1	100	48
9	24.4	47	24.4	100	48	24.0	98	47
10	25.0	47	24.9	100	48	24.6	98	47
11	25.0	47	24.9	100	48	25.1	100	47
12	24.9	47	24.8	100	48	24.9	100	47
14	25.7	47	26.0	101	48	25.9	101	47
19	26.3	46	26.5	101	48	27.0	103	47
23	29.3	45	28.4	97	48	29.1	99	46
27	31.3	45	30.2	96	48	31.0	99	46
32	33.0	45	31.9	97	48	32.7	99	46
34	34.1	45	33.4	98	48	34.5	101	46
38	35.4	45	34.1	96	48	35.9	101	46
42	35.7	44	33.8	95	48	35.2	99	46
46	37.2	44	35.8	96	47	35.2	95	46
50	37.2	44	34.7	93	47	36.3	98	46
54	38.0	44	35.2	93	47	37.3	98	46
58	38.9	44	36.2	93	47	38.2	98	46
62	39.9	43	37.4	94	46	39.4	99	46
66	40.2	42	38.9	97	45	40.3	100	46
70	39.6	42	37.9	96	44	40.1	101	46
74	42.0	38	40.3	96	42	41.4	99	46
79	42.4	36	42.2	100	40	43.6	103	45
82	42.8	35	41.0	96	38	42.1	98	45
86	42.4	32	42.5	100	37	43.1	102	45
94	44.0	30	43.3	98	34	41.5	94	42
98	43.9	28	42.3	96	33	43.9	100	39
102	43.3	28	41.6	96	32	42.8	99	38

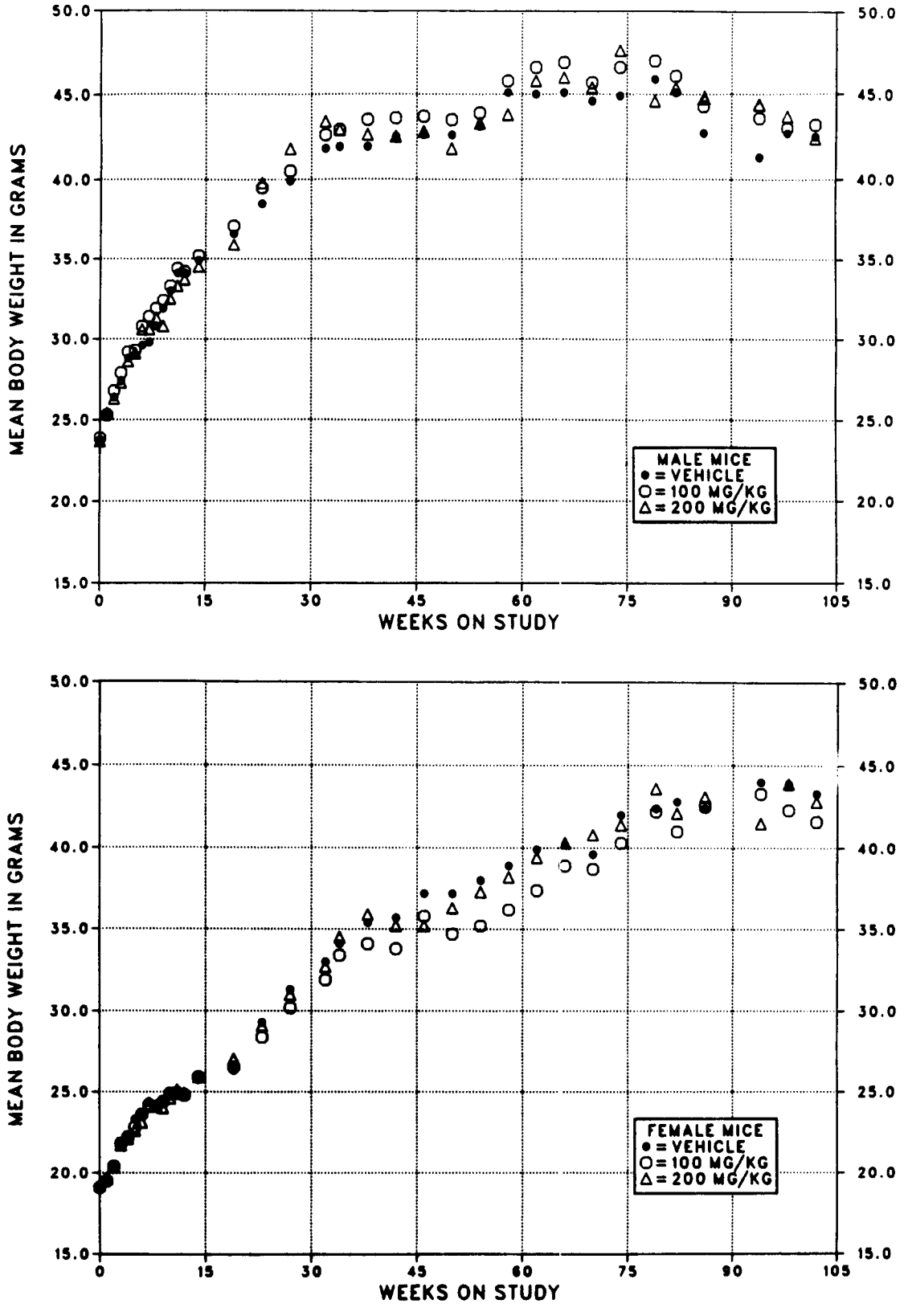


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED BENZYL ALCOHOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered benzyl alcohol at the doses used in these studies and for vehicle controls are shown in Table 14 and in the Kaplan and Meier curves in Figure 6. The survival of the female vehicle controls was significantly lower than that of the high dose group after week 74. No other differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the brain, adrenal gland, harderian gland, and lung.

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 14. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	11	9
Accidentally killed (c)	4	6	6
Killed at termination	34	33	35
Survival P values (d)	0.506	0.960	0.592
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	17	9
Accidentally killed (e)	4	1	5
Killed at termination	25	31	36
Died during termination period	1	1	0
Survival P values (d)	0.012	0.537	0.013

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) All but one death were judged to be related to the gavage procedures.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(e) All deaths were judged to be related to the gavage procedures.

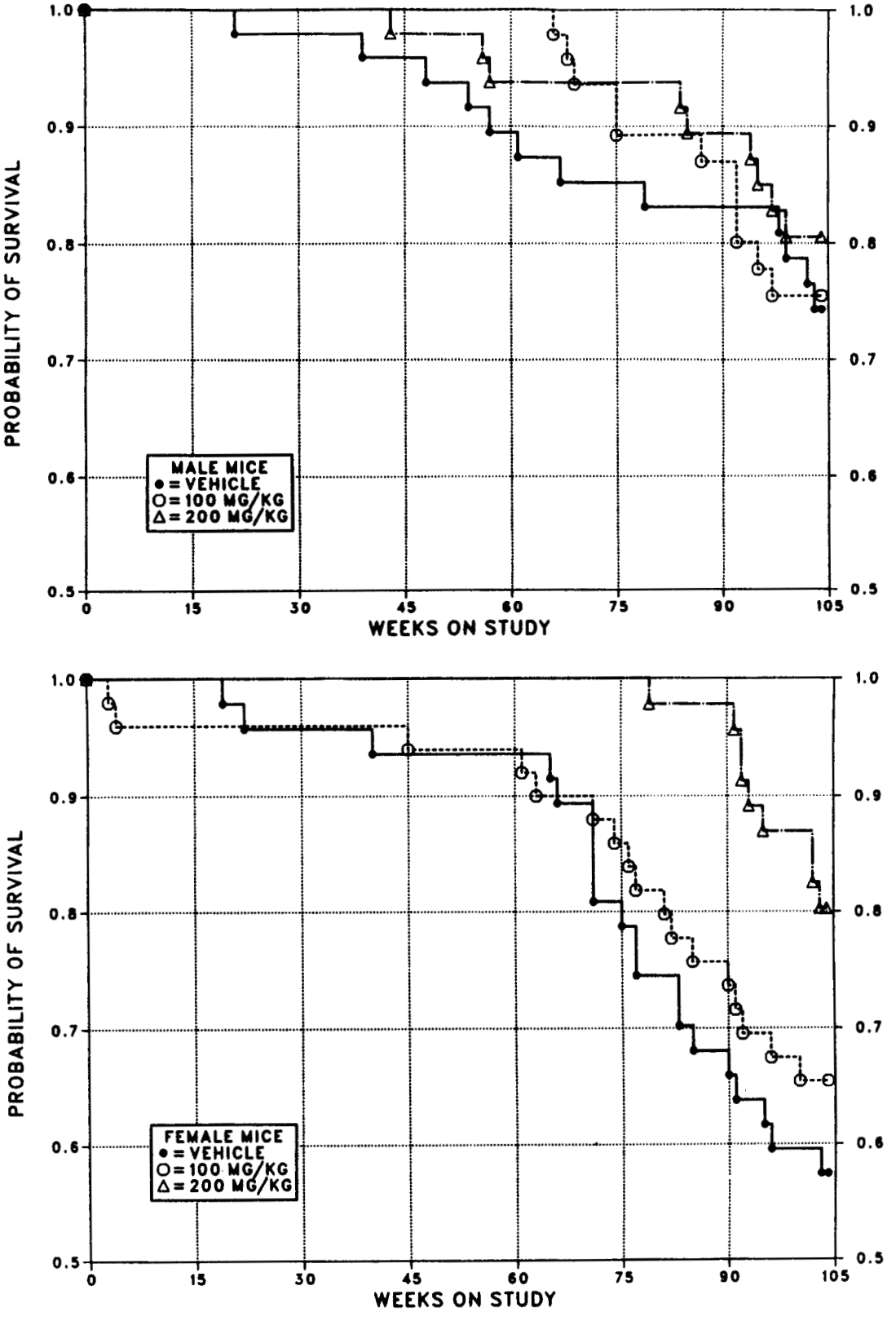


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED BENZYL ALCOHOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Brain: Corpora amylacea was observed at an increased incidence in high dose male and female mice (male: vehicle control, 15/49; low dose, 21/48; high dose, 22/50; female: 14/50; 15/48; 25/50). This lesion consisted of one or several small foci of mineralization in the thalamus and is a common, spontaneously occurring lesion.

Adrenal Gland: Adenomas of the adrenal cortex occurred at a slightly increased incidence in high dose male mice ($P = 0.044$, life table and incidental tumor tests). These tumors are relatively uncommon in historical controls receiving corn oil by gavage (20/1,687, 1%), but three in a group is within the historical range. This slight increase is not considered to be compound related.

Harderian Gland: Adenomas in male mice occurred with a negative trend (vehicle control, 8/50; low dose, 3/50; high dose, 2/50; $P = 0.027$, incidental tumor test); the incidences in the dosed groups were not significantly different from that in the vehicle controls by the incidental tumor test ($P = 0.057$).

Lung: Congestion was observed at an increased incidence in high dose male mice (male: vehicle control, 1/50; low dose, 1/48; high dose, 4/50; female: 1/50; 1/19; 0/50). Foreign material was observed at increased incidences in low dose mice (male: 2/50; 7/48; 4/50; female: 3/50; 7/19; 4/50). The increased incidences were not statistically significant.

IV. DISCUSSION AND CONCLUSIONS

The most prominent clinical signs observed in rats and mice during the 16-day and 13-week studies were postgavage lethargy and staggering, and hemorrhage from the mouth and nose and in the gastrointestinal and urinary tracts. These responses were not unexpected, since benzyl alcohol is used as a topical anesthetic and was shown to induce a spectrum of behavioral responses identical to that from ethyl alcohol intoxication (McCreery and Hunt, 1978). Benzyl alcohol is also used as a preservative in medicinal products and was identified as the component associated with brain hemorrhage in neonatal infants (Menon et al., 1984; Benda et al., 1986), reportedly causing erythrocyte fragmentation and hemolysis (Nwafor and Coakley, 1986).

Benzyl alcohol was suspected as the causative agent in parenteral preparations administered to neonatal infants, causing the "gasping syndrome." McCloskey et al. (1986) studied this syndrome in mice and showed that the acute toxic symptoms from benzyl alcohol, including sedation, dyspnea, and loss of motor function, were due to the parent compound and not to metabolites; inhibition of alcohol dehydrogenase with pyrazole increased circulating benzyl alcohol levels and caused a marked increase in toxicity.

The demonstrable neurotoxic effects (lethargy and staggering) of benzyl alcohol were a strong consideration in the selection of doses for the 2-year studies in rats (0, 200, and 400 mg/kg) and mice (0, 100, and 200 mg/kg). Since there were no changes in body weight in mice in the 2-year studies and no notable difference in mortality rates between exposed groups and vehicle controls, somewhat higher doses for the 2-year studies might have been used. The lower doses were selected based on reduction in body weight gain at 400 and 800 mg/kg and because of the potential contribution of the anesthetic properties of benzyl alcohol to the gavage-related deaths.

Even though the short-term toxicity data did not suggest any contraindications, survival was poor in the female rats; mortality in the second year of the study was greater in the chemically exposed rats than in the vehicle controls. At study termination, only 17 animals were alive in each of the dosed groups, but 25 low dose and 29 high dose females were alive at week 85, and 20 and 21 were alive at week 101. It is believed that adequate numbers of animals had been exposed long enough to benzyl alcohol for any potential carcinogenic activity to have been detected.

During the 2-year studies, gavage procedures affected the pulmonary tract in male rats in a dose-related manner, with an increase in acute inflammation in the nasal tract, hemorrhage in the larynx, and edema, hemorrhage, and foreign material in the lungs. The incidences of hemorrhage and foreign material in the lungs also increased in dosed female rats. In male mice, the incidences of congestion and foreign material in the lungs were slightly increased. It is not possible to determine retrospectively whether these effects were the result of gavage "accidents" with direct deposition of material within the lung or due to the anesthetic properties of benzyl alcohol, with reflux of the gavage material and aspiration into the lungs. Either condition could be a contributory factor to the difficulties encountered with the gavage route of administration.

Benzyl alcohol is readily absorbed from the gastrointestinal tract after gavage administration and is rapidly oxidized to benzoic acid (Williams, 1959), just as is benzyl acetate, which is initially converted to benzyl alcohol after gavage administration (Chidgey et al., 1986). At lower doses, benzoic acid is then conjugated with glycine and excreted in the urine as hippuric acid. Hippuric acid is also the primary (>95%) metabolite of benzyl acetate at doses up to 1,000 mg/kg (Abdo et al., 1985). Earlier toxicity and carcinogenesis studies of benzyl acetate were conducted by gavage in corn oil at doses of 500 or 1,000 mg/kg in F344/N rats and at 250 or 500 mg/kg in $B6C3F_1$ mice (Abdo et al., 1985; NTP, 1986). (These molar doses are equivalent to 360 and 720 mg/kg benzyl alcohol for rats and 180 and 360 mg/kg for mice.) Benzyl acetate was associated with increased incidences of acinar cell adenomas of the exocrine pancreas in male rats and increased incidences of hepatocellular neoplasms (particularly adenomas) and squamous cell neoplasms of the forestomach in mice of each sex. Body weights and survival were also unaffected in those studies, except for mortality in low dose female mice which may have been related to

utero-ovarian infections. Inasmuch as both benzyl alcohol and benzyl acetate share a common metabolite, benzoic acid, and benzyl acetate is initially and rapidly metabolized to benzyl alcohol, the parent benzyl acetate molecule seems to have been the effective carcinogen.

There is no obvious structural indication that benzyl alcohol will react with cellular DNA (Miller and Miller, 1977; Ashby, 1985). Results of assays for mutagenic activity in bacteria were uniformly negative in both the presence and absence of metabolic activation. Some evidence of genetic toxicity was observed in the three in vitro assays conducted in cultured mammalian cells. A dose-related increase was observed in the sister chromatid exchange (SCE) assay in Chinese hamster ovary (CHO) cells in one of two trials conducted in both the presence and absence of metabolic activation. This response was considered weakly positive because the increase in SCEs was significantly elevated over the control only at the highest dose level. The overall result of the test was concluded to be equivocal because the weak positive response obtained was not reproduced. The results of the chromosomal aberration test in CHO cells showed a reproducible, increased number of cells with aberrations in the presence of S9 only at a relatively high dose of 4,000 µg/ml. The L5178Y mouse lymphoma assay for trifluorothymidine (Tft) resistance yielded, in the absence of S9, elevated frequencies of resistant colonies, but the effect was associated with high toxicity. These limited, positive effects of benzyl alcohol in tests with cultured mammalian cells, which either were generally weak, occurred only at very high doses, lacked reproducibility, or exhibited inconsistencies in the S9 requirement, do not permit a definitive conclusion regarding the genetic toxicity of benzyl alcohol.

α-Methylbenzyl alcohol, an analog of benzyl alcohol, was given mistakenly to animals at week 80 in the 2-year studies. α-Methylbenzyl alcohol, like benzyl alcohol, did not induce reverse mutations in Salmonella but did increase the frequency of Tft-resistant colonies in the mouse lymphoma assay in the absence of S9 and induced chromosomal aberrations in CHO cells in the presence of S9. α-Methylbenzyl alcohol, unlike benzyl alcohol, did not increase the frequencies of SCEs in CHO cells, either with or without metabolic activation.

Benzyl acetate, a chemical that has benzyl alcohol as one of its metabolites after oral administration to rats and mice, has even less genotoxic activity than was observed for benzyl alcohol. In NTP tests, benzyl acetate was not mutagenic in Salmonella, nor did it induce SCEs or chromosomal aberrations in CHO cells, with or without metabolic activation, but it did increase the frequency of Tft-resistant colonies in the L5178Y mouse lymphoma assay in the presence but not absence of liver S9 (NTP, 1986).

Three metabolites of benzyl alcohol--benzaldehyde, benzoic acid, and hippuric acid--have been tested for genotoxicity. The data suggest that, as with benzyl alcohol, these related compounds are not strong mutagens (Kikuchi et al., 1977; Simmon and Kauhanen, 1978; Haworth et al., 1983), but evidence of clastogenicity was reported for benzaldehyde. Kasamaki et al. (1982) reported that benzaldehyde induced chromosomal aberrations in cultured CHO cells, but this response was not observed in NTP cytogenetic assays with CHO cells at up to 1,600 µg/ml with S9 activation (Galloway et al., 1987). However, Galloway et al. did report positive responses to benzaldehyde in the SCE assay, with and without S9 activation. Benzaldehyde also induced forward mutations at the $TK^{+/-}$ locus of mouse L5178Y cells in the absence of S9 (McGregor et al., 1989).

The experimental and tabulated data for the NTP Technical Report on benzyl alcohol were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, 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.

IV. DISCUSSION AND CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of benzyl alcohol for male or female F344/N rats dosed with 200 or 400 mg/kg. Survival in both dose groups of female rats was 50% that of vehicle controls, primarily due to an increased number of gavage-related deaths. There was *no evidence of carcinogenic activity* of benzyl alcohol for male or female $B6C3F_1$ mice dosed with 100 or 200 mg/kg for 2 years.

*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.

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APPENDIX A

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS	2 (4%)	1 (2%)	1 (2%)
Basal cell tumor	1 (2%)		1 (2%)
Trichoepithelioma	1 (2%)		1 (2%)
Keratoacanthoma	3 (6%)	2 (4%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	2 (4%)	2 (4%)
Myxoma			1 (2%)
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(49)	(15)	(49)
Sarcoma, NOS			1 (2%)
#Lung	(50)	(18)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma			1 (2%)
Sarcoma, NOS, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	15 (30%)	9 (18%)	10 (20%)
#Liver	(50)	(26)	(50)
Leukemia, mononuclear cell		2 (8%)	
#Thymus	(45)	(12)	(48)
Thymoma, benign			1 (2%)
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(16)	(44)
Myxosarcoma		1 (6%)	
#Liver	(50)	(26)	(50)
Neoplastic nodule	1 (2%)		1 (2%)
Hepatocellular carcinoma	1 (2%)		
#Pancreas	(47)	(14)	(50)
Acinar cell adenoma			1 (2%)
#Esophagus	(50)	(15)	(50)
Sarcoma, NOS, invasive			1 (2%)
#Forestomach	(48)	(19)	(50)
Squamous cell papilloma		1 (5%)	1 (2%)
URINARY SYSTEM			
None			

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	18 (37%)	18 (37%)	13 (26%)
#Adrenal medulla	(50)	(15)	(50)
Pheochromocytoma	19 (38%)	2 (13%)	18 (36%)
Pheochromocytoma, malignant	1 (2%)	1 (7%)	1 (2%)
#Thyroid	(49)	(16)	(49)
Follicular cell adenoma	1 (2%)		2 (4%)
Follicular cell carcinoma		2 (13%)	2 (4%)
C-cell adenoma	1 (2%)		2 (4%)
C-cell carcinoma	3 (6%)		1 (2%)
#Parathyroid	(39)	(7)	(40)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(47)	(14)	(50)
Islet cell adenoma	1 (2%)		2 (4%)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
Fibroadenoma		2 (4%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
#Testis	(49)	(42)	(49)
Interstitial cell tumor	39 (80%)	31 (74%)	33 (67%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(14)	(50)
Granular cell tumor, NOS	1 (2%)		
Glioma, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*External ear	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		1 (2%)
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Mesentery	(50)	(50)	(50)
Lipoma			1 (2%)
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		4 (8%)
ALL OTHER SYSTEMS			
Tail			
Keratoacanthoma			1

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	17	14	11
Moribund sacrifice	1	1	1
Terminal sacrifice	28	27	24
Dosing accident	4	7	14
Accidentally killed, nda		1	
TUMOR SUMMARY			
Total animals with primary tumors**	48	39	41
Total primary tumors	117	76	113
Total animals with benign tumors	45	38	35
Total benign tumors	88	61	92
Total animals with malignant tumors	24	13	16
Total malignant tumors	25	15	16
Total animals with secondary tumors##	1		1
Total secondary tumors	1		2
Total animals with tumors uncertain-- benign or malignant	3		5
Total uncertain tumors	4		5

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 BENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 95	10 0	C 63	C 59	C 89	C 60	C 69	C 81	C 78	C 65	C 84	C 67	C 68	C 58	C 96	C 73	C 97	C 53	C 87	C 57	C 82	C 51	C 52	C 54	C 55
WEEKS ON STUDY	00 4	01 1	05 9	06 0	07 0	07 6	08 1	08 5	08 6	08 9	08 9	09 1	09 3	09 4	09 4	09 5	09 5	09 6	09 8	09 9	10 1	10 2	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									X
Basal cell tumor																									
Trichoepithelioma																									X
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Nasal cavity	+	+	+	–	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Small intestine	+	+	+	–	+	+	+	+	–	+	–	+	+	~	+	+	+	–	+	+	+	+	+	+	+
Large intestine	+	+	+	–	+	+	+	+	–	+	–	+	+	~	+	+	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	–	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	–	+	+	+	+	~	+	+	+	–	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS				X				X			X	X			X				X			X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X	X	X	X		X		X		X
Pheochromocytoma, malignant									X																
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular cell adenoma				X																					
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	–	+	+	+	–	+	–	+	+	–	+	+	+	+	–	+	+	+	+	–
Pancreatic islets	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	N	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Interstitial cell tumor						X	X	X	X	X			X	X		X	X		X	X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Glioma, NOS														X											
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Squamous cell carcinoma					X																				
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Carcinoma, NOS																								X	
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS										X															
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Mesothelioma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X			X						X			X					X	X			

+: Tissue examined microscopically
~: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	C 5 6	C 6 1	C 6 2	C 6 4	C 6 6	C 7 0	C 7 1	C 7 2	C 7 4	C 7 5	C 7 6	C 7 7	C 7 9	C 8 0	C 8 3	C 8 5	C 8 6	C 8 8	C 9 0	C 9 1	C 9 2	C 9 3	C 9 4	C 9 8	C 9 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS	X																									2
Basal cell tumor									X																	1
Trichoepithelioma																										1
Keratoacanthoma		X													X			X								3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma								X																		2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X																			1
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																			X							1
Adenoma, NOS			X	X						X		X	X	X	X						X		X			18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X				X		X	X	X	X			X	X	X	X				X		X			19
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
C-cell adenoma																									X	1
C-cell carcinoma										X		X						X								3
Parathyroid	−	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma				X																						1
Islet cell carcinoma		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	N	+	N	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS											X															1
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell						X						X		X	X	X	X			X		X			X	15

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: LOW DOSE

ANIMAL NUMBER	C 7 8	C 9 7	C 5 7	C 9 5	C 5 6	C 6 6	C 7 9	C 7 1	C 9 3	C 7 7	C 8 8	C 5 9	C 7 2	C 8 3	C 9 4	C 6 8	C 7 6	C 8 4	1 0 0	C 8 0	C 6 0	C 8 9	C 9 2	C 5 1	C 5 2
WEEKS ON STUDY	0 1 5	0 1 6	0 2 1	0 2 4	0 4 0	0 4 1	0 4 1	0 4 2	0 4 9	0 5 5	0 7 9	0 8 9	0 8 9	0 9 1	0 9 7	0 9 8	0 9 9	1 0 0	1 0 0	1 0 1	1 0 2	1 0 2	1 0 3	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS													X												
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	+	–	–	–	–
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–
Nasal cavity	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	–	+	–
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	–	–	–	–	–	–	–
Thymus	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	+	–	–	–	–	–	–	–
Myxosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	+	–	–
Leukemia, mononuclear cell																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	+	–	–
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	+	–	–	+	–
Squamous cell papilloma																								X	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–	–	–	–
Large intestine	+	+	+	+	–	+	+	+	+	+	+	–	+	–	–	–	–	+	–	–	+	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	+	+	–	–	–	–
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X		X		X		X		X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	–	–
Pheochromocytoma												X		X											
Pheochromocytoma, malignant																X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–
Follicular cell carcinoma															X										
Parathyroid	–	–	–	+	+	+	–	–	+	–	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	–	–	–	+	+	+	+
Interstitial cell tumor											X	X	X		X			X					X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–	–	–
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell													X	X	X	X	X	X							

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	C 5 3	C 5 4	C 5 5	C 5 8	C 6 1	C 6 2	C 6 3	C 6 4	C 6 5	C 6 7	C 6 9	C 7 0	C 7 3	C 7 4	C 7 5	C 8 1	C 8 2	C 8 5	C 8 6	C 8 7	C 9 0	C 9 1	C 9 6	C 9 8	C 9 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	+	N	N	N	*50
Papilloma, NOS																										1
Keratoacanthoma																		X				X				2
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	+	N	N	N	*50
Fibroma					X						X															2
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	18
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Spleen	–	–	–	+	+	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	24
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	16
Myxosarcoma														X												1
Liver	–	–	–	+	–	–	–	–	–	–	–	+	–	+	–	–	–	–	+	–	–	+	+	–	+	26
Leukemia, mononuclear cell																							X			2
Bile duct	–	–	–	+	–	–	–	–	–	–	–	+	–	+	–	–	–	–	+	–	–	+	+	–	+	26
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Stomach	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	19
Squamous cell papilloma																										1
Small intestine	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	14
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	+	–	–	–	+	+	–	–	–	–	–	–	–	–	+	+	–	–	–	22
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X			X	X	X	X	X									X	X		X	X	X		18
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Pheochromocytoma																										2
Pheochromocytoma, malignant																										1
Thyroid	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
Follicular cell carcinoma							X																			2
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	N	N	N	N	N	N	+	*50	
Adenoma, NOS																									X	1
Fibroadenoma											X				X											2
Testis	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	42
Interstitial cell tumor	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	31
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																	X									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell				X								X							X						9

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: HIGH DOSE

ANIMAL NUMBER	C 8 1	C 5 2	C 5 4	C 6 2	C 6 8	C 7 8	C 9 0	C 5 5	C 8 9	C 9 3	C 9 9	C 9 1	C 8 3	C 7 2	C 5 9	C 6 6	C 9 6	C 6 9	C 6 1	C 7 9	C 5 1	C 9 8	C 7 1	C 8 7	C 5 8
WEEKS ON STUDY	0 0 0	0 0 1	0 0 9	0 0 9	0 4 8	0 4 8	0 4 8	0 4 9	0 5 5	0 5 7	0 6 5	0 7 5	0 7 8	0 8 0	0 8 5	0 8 9	0 9 2	0 9 3	0 9 5	0 9 5	0 9 6	0 9 7	0 9 8	0 9 8	1 0 0
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Basal cell tumor																									
Trichoepithelioma																									
Keratoacanthoma																						X			
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																					X				X
Myxoma																									
Lipoma																									
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Sarcoma, NOS, metastatic												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Sarcoma, NOS												X													
Nasal cavity	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	−	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, invasive												X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+
Large intestine	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	C64	C53	C56	C57	C60	C63	C65	C67	C70	C73	C74	C75	C76	C77	C80	C82	C84	C85	C86	C88	C92	C94	C95	C97	100	TOTAL:
WEEKS ON STUDY	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS													X													1
Basal cell tumor																				X						1
Trichoepithelioma															X											1
Keratoacanthoma					X					X																3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										2
Myxoma					X																					1
Lipoma		X																								1
Hemangioma												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																					1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma, benign																									X	1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																		X								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma					X																					1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, invasive																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma					X																					1
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	C81	C52	C54	C62	C68	C78	C90	C55	C89	C93	C99	C91	C83	C72	C59	C66	C96	C69	C61	C79	C51	C98	C71	C87	C58
WEEKS ON STUDY	000	001	009	009	048	048	048	049	055	057	065	075	078	080	085	089	092	093	095	093	096	097	098	098	100
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X	X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X	X				X				
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																							X		
C-cell adenoma																X									
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	−
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																						+ X			
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Interstitial cell tumor														X		X		X	X	X	X	X			X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS									X																
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Mesothelioma, NOS								X						X											
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell											X		X		X		X	X	X		X				
Tail																									
Keratoacanthoma																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	C 6 4	C 5 3	C 5 6	C 5 7	C 6 0	C 6 3	C 6 5	C 6 7	C 7 0	C 7 3	C 7 4	C 7 5	C 7 6	C 7 7	C 8 0	C 8 2	C 8 4	C 8 5	C 8 6	C 8 8	C 9 2	C 9 4	C 9 5	C 9 7	1 0 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X	X		X					X	X	X		X	X			X		X	X		13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X				X	X		X			X	X	X	X	X	X	X				X	X	X	18
Pheochromocytoma, malignant														X												1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X															X								2
Follicular cell carcinoma																									X	2
C-cell adenoma																						X				2
C-cell carcinoma													X													1
Parathyroid	−	+	+	+	−	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	40
Adenoma, NOS		X																								1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma															X											2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Fibroadenoma												X	X									X				3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	33
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	*50
Carcinoma, NOS				X																						1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																	X						X			4
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma						X																				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X						X																	X		10
Tail																										
Keratoacanthoma										X																1

* Animals necropsied

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

	Vehicle Control	200 mg/kg	400 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	10.7%	7.4%	11.5%
Terminal Rates (c)	3/28 (11%)	2/27 (7%)	2/24 (8%)
Week of First Observation	104	104	97
Life Table Tests (d)	P=0.521	P=0.517N	P=0.595
Incidental Tumor Tests (d)	P=0.520	P=0.517N	P=0.594
Cochran-Armitage Trend Test (d)	P=0.588		
Fisher Exact Test (d)		P=0.500N	P=0.661
Subcutaneous Tissue: Fibroma or Myxoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	6.5%	7.4%	10.9%
Terminal Rates (c)	1/28 (4%)	2/27 (7%)	1/24 (4%)
Week of First Observation	96	104	96
Life Table Tests (d)	P=0.350	P=0.692	P=0.442
Incidental Tumor Tests (d)	P=0.350	P=0.675	P=0.442
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.691	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/50 (30%)	(e,f) 11/50 (22%)	10/50 (20%)
Adjusted Rates (b)	42.4%		28.4%
Terminal Rates (c)	9/28 (32%)		2/24 (8%)
Week of First Observation	59		65
Life Table Test (d)			P=0.326N
Incidental Tumor Test (d)			P=0.269N
Fisher Exact Test (d)			P=0.178N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	18/49 (37%)	18/49 (37%)	13/50 (26%)
Adjusted Rates (b)	49.8%	53.7%	49.0%
Terminal Rates (c)	11/28 (39%)	11/26 (42%)	11/24 (46%)
Week of First Observation	60	89	92
Life Table Tests (d)	P=0.334N	P=0.516	P=0.362N
Incidental Tumor Tests (d)	P=0.333N	P=0.366	P=0.364N
Cochran-Armitage Trend Test (d)	P=0.151N		
Fisher Exact Test (d)		P=0.583N	P=0.175N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	19/49 (39%)	18/49 (37%)	13/50 (26%)
Adjusted Rates (b)	52.7%	53.7%	49.0%
Terminal Rates (c)	12/28 (43%)	11/26 (42%)	11/24 (46%)
Week of First Observation	60	89	92
Life Table Tests (d)	P=0.266N	P=0.563N	P=0.291N
Incidental Tumor Tests (d)	P=0.261N	P=0.447	P=0.290N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Test (d)		P=0.500N	P=0.126N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	(f) 2/15 (13%)	18/50 (36%)
Adjusted Rates (b)	57.2%		65.8%
Terminal Rates (c)	14/28 (50%)		15/24 (63%)
Week of First Observation	95		89
Life Table Test (d)			P=0.439
Incidental Tumor Test (d)			P=0.414
Fisher Exact Test (d)			P=0.500N

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

	Vehicle Control	200 mg/kg	400 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	20/50 (40%)	(f) 3/15 (20%)	18/50 (36%)
Adjusted Rates (b)	58.2%		65.8%
Terminal Rates (c)	14/28 (50%)		15/24 (63%)
Week of First Observation	86		89
Life Table Test (d)			P=0.517
Incidental Tumor Test (d)			P=0.487
Fisher Exact Test (d)			P=0.419N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	(f) 2/16 (13%)	4/49 (8%)
Adjusted Rates (b)	2.1%		15.6%
Terminal Rates (c)	0/28 (0%)		3/24 (13%)
Week of First Observation	60		98
Life Table Test (d)			P=0.140
Incidental Tumor Test (d)			P=0.161
Fisher Exact Test (d)			P=0.181
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	3/49 (6%)	(f) 0/16 (0%)	1/49 (2%)
Adjusted Rates (b)	10.7%		4.2%
Terminal Rates (c)	3/28 (11%)		1/24 (4%)
Week of First Observation	104		104
Life Table Test (d)			P=0.360N
Incidental Tumor Test (d)			P=0.360N
Fisher Exact Test (d)			P=0.309N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	(f) 0/16 (0%)	3/49 (6%)
Adjusted Rates (b)	14.3%		11.0%
Terminal Rates (c)	4/28 (14%)		2/24 (8%)
Week of First Observation	104		89
Life Table Test (d)			P=0.585N
Incidental Tumor Test (d)			P=0.604N
Fisher Exact Test (d)			P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	7.4%	12.5%
Terminal Rates (c)	0/28 (0%)	2/27 (7%)	3/24 (13%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.059	P=0.230	P=0.094
Incidental Tumor Tests (d)	P=0.059	P=0.230	P=0.094
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	11.1%	12.5%
Terminal Rates (c)	0/28 (0%)	3/27 (11%)	3/24 (13%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.072	P=0.113	P=0.094
Incidental Tumor Tests (d)	P=0.072	P=0.113	P=0.094
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121

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

	Vehicle Control	200 mg/kg	400 mg/kg
Testis: Interstitial Cell Tumor			
Overall Rates (a)	39/49 (80%)	31/42 (74%)	33/49 (67%)
Adjusted Rates (b)	97.4%	100.0%	100.0%
Terminal Rates (c)	27/28 (96%)	25/25 (100%)	24/24 (100%)
Week of First Observation	76	79	80
Life Table Tests (d)	P=0.471N	P=0.187N	P=0.534N
Incidental Tumor Tests (d)	P=0.571	P=0.377	P=0.623N
Cochran-Armitage Trend Test (d)	P=0.104N		
Fisher Exact Test (d)		P=0.343N	P=0.126N
All Sites: Mesothelioma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	2.4%	0.0%	12.9%
Terminal Rates (c)	0/28 (0%)	0/27 (0%)	2/24 (8%)
Week of First Observation	89		49
Life Table Tests (d)	P=0.065	P=0.510N	P=0.143
Incidental Tumor Tests (d)	P=0.069	P=0.581N	P=0.173
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
All Sites: Benign Tumors			
Overall Rates (a)	45/50 (90%)	38/50 (76%)	35/50 (70%)
Adjusted Rates (b)	97.8%	100.0%	100.0%
Terminal Rates (c)	27/28 (96%)	27/27 (100%)	24/24 (100%)
Week of First Observation	60	79	55
Life Table Tests (d)	P=0.235N	P=0.183N	P=0.286N
Incidental Tumor Tests (d)	P=0.097N	P=0.319N	P=0.135N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.055N	P=0.012N
All Sites: Malignant Tumors			
Overall Rates (a)	24/50 (48%)	13/50 (26%)	16/50 (32%)
Adjusted Rates (b)	63.4%	36.8%	45.0%
Terminal Rates (c)	15/28 (54%)	6/27 (22%)	6/24 (25%)
Week of First Observation	59	89	65
Life Table Tests (d)	P=0.180N	P=0.039N	P=0.238N
Incidental Tumor Tests (d)	P=0.124N	P=0.080N	P=0.157N
Cochran-Armitage Trend Test (d)	P=0.058N		
Fisher Exact Test (d)		P=0.019N	P=0.076N
All Sites: All Tumors			
Overall Rates (a)	48/50 (96%)	39/50 (78%)	41/50 (82%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	28/28 (100%)	27/27 (100%)	24/24 (100%)
Week of First Observation	59	79	49
Life Table Tests (d)	P=0.485N	P=0.114N	P=0.540N
Incidental Tumor Tests (d)	P=0.353N	P=0.098N	P=0.369N
Cochran-Armitage Trend Test (d)	P=0.033N		
Fisher Exact Test (d)		P=0.008N	P=0.026N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Only 24 spleens were examined microscopically.
(f) Incomplete sampling of tissues

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Epidermal inclusion cyst			1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic focal			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(46)	(1)	(47)
Foreign body, NOS			1 (2%)
Inflammation, acute	2 (4%)		5 (11%)
Infection, fungal	3 (7%)		2 (4%)
*Larynx	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Hemorrhage	1 (2%)	1 (2%)	5 (10%)
Inflammation, active chronic	1 (2%)		
#Trachea	(49)	(15)	(49)
Hemorrhage		1 (7%)	
Inflammation, acute			1 (2%)
#Lung/bronchus	(50)	(18)	(50)
Inflammation, acute suppurative	1 (2%)		
Polyp, inflammatory			1 (2%)
#Lung	(50)	(18)	(50)
Vegetable foreign body		1 (6%)	
Congestion, NOS	2 (4%)	2 (11%)	3 (6%)
Edema, NOS	1 (2%)	1 (6%)	5 (10%)
Hemorrhage	2 (4%)	3 (17%)	8 (16%)
Bronchopneumonia, acute			2 (4%)
Abscess, NOS			1 (2%)
Pneumonia, interstitial chronic	4 (8%)		
Inflammation, chronic focal	1 (2%)		2 (4%)
Inflammation, granulomatous focal		1 (6%)	
Granuloma, foreign body	1 (2%)		1 (2%)
Foreign material, NOS	1 (2%)	7 (39%)	13 (26%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, adenomatous	9 (18%)	1 (6%)	5 (10%)
Metaplasia, osseous			2 (4%)
Histiocytosis	23 (46%)	4 (22%)	19 (38%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(14)	(50)
Hyperplasia, NOS			1 (2%)
Myelofibrosis	1 (2%)		
Hyperplasia, reticulum cell			1 (2%)
#Spleen	(49)	(24)	(50)
Congestion, NOS		2 (8%)	1 (2%)
Fibrosis		1 (4%)	
Fibrosis, focal	1 (2%)		3 (6%)
Fibrosis, multifocal		1 (4%)	
Lipoidosis		1 (4%)	
Pigmentation, NOS	14 (29%)	2 (8%)	12 (24%)
#Splenic capsule	(49)	(24)	(50)
Fibrosis	1 (2%)		

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(50)	(16)	(50)
Cyst, NOS	3 (6%)		2 (4%)
Hemorrhage	2 (4%)		1 (2%)
#Mediastinal lymph node	(50)	(16)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute			1 (2%)
Necrosis, diffuse			1 (2%)
Foreign material, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
#Mesenteric lymph node	(50)	(16)	(50)
Cyst, NOS			2 (4%)
Edema, NOS	1 (2%)		
Hemorrhage	2 (4%)		
Metaplasia, osseous			1 (2%)
#Thymus	(45)	(12)	(48)
Hemorrhage		1 (8%)	1 (2%)
Hyperplasia, epithelial			1 (2%)
CIRCULATORY SYSTEM			
#Brain/meninges	(50)	(14)	(50)
Thrombosis, NOS			1 (2%)
#Cerebrum	(50)	(14)	(50)
Embolism, NOS	1 (2%)		
#Spleen	(49)	(24)	(50)
Thrombosis, NOS			1 (2%)
#Lung	(50)	(18)	(50)
Thrombosis, NOS		2 (11%)	
#Heart	(50)	(15)	(50)
Myxomatosis, cardiac valve			1 (2%)
Embryonal duct cyst	1 (2%)		
Mineralization			1 (2%)
Thrombosis, NOS	2 (4%)		
Inflammation, chronic	2 (4%)	7 (47%)	7 (14%)
Fibrosis, focal	4 (8%)		
Fibrosis, multifocal	32 (64%)	4 (27%)	32 (64%)
#Heart/atrium	(50)	(15)	(50)
Thrombosis, NOS	1 (2%)	1 (7%)	
#Myocardium	(50)	(15)	(50)
Degeneration, NOS		1 (7%)	
#Endocardium	(50)	(15)	(50)
Thrombosis, NOS		1 (7%)	
Inflammation, chronic focal	1 (2%)		
Fibrosis, diffuse	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute focal		1 (2%)	
#Adrenal	(50)	(15)	(50)
Thrombosis, NOS			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Salivary gland	(47)	(16)	(44)
Inflammation, active chronic		1 (6%)	
Inflammation, chronic	2 (4%)	1 (6%)	1 (2%)
Metaplasia, squamous	1 (2%)		

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Parotid gland	(47)	(16)	(44)
Inflammation, active chronic	1 (2%)		
Atrophy, diffuse	1 (2%)		
#Liver	(50)	(26)	(50)
Cyst, NOS			1 (2%)
Congestion, NOS	1 (2%)		
Congestion, acute passive	1 (2%)		
Congestion, chronic passive		1 (4%)	
Inflammation, acute		1 (4%)	2 (4%)
Inflammation, acute focal		1 (4%)	
Inflammation, acute/chronic		1 (4%)	
Inflammation, chronic		1 (4%)	
Inflammation, chronic focal	1 (2%)		
Peliosis hepatis	9 (18%)	3 (12%)	6 (12%)
Basophilic cyto change	20 (40%)		18 (36%)
Cytologic alteration, NOS	5 (10%)	2 (8%)	4 (8%)
Hyperplastic nodule	1 (2%)	3 (12%)	
#Portal tract	(50)	(26)	(50)
Inflammation, acute			1 (2%)
#Liver/centrilobular	(50)	(26)	(50)
Congestion, NOS			1 (2%)
Necrosis, diffuse	2 (4%)	5 (19%)	1 (2%)
Cytoplasmic vacuolization	2 (4%)		
#Liver/periportal	(50)	(26)	(50)
Cytoplasmic vacuolization	1 (2%)		
#Bile duct	(50)	(26)	(50)
Hyperplasia, NOS	41 (82%)	13 (50%)	30 (60%)
#Pancreas	(47)	(14)	(50)
Cyst, NOS	1 (2%)		
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal	3 (6%)		1 (2%)
Scar			1 (2%)
Cytoplasmic vacuolization	1 (2%)		1 (2%)
#Pancreatic acinus	(47)	(14)	(50)
Atrophy, NOS	2 (4%)		
Atrophy, focal	6 (13%)	1 (7%)	5 (10%)
Atrophy, diffuse	2 (4%)		
Hyperplasia, focal			1 (2%)
#Esophagus	(50)	(15)	(50)
Vegetable foreign body		1 (7%)	
Hemorrhage	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Granuloma, NOS		1 (7%)	
#Esophagus/muscularis	(50)	(15)	(50)
Regeneration, NOS			1 (2%)
#Esophageal adventitia	(50)	(15)	(50)
Inflammation, chronic			1 (2%)
#Glandular stomach	(48)	(19)	(50)
Ulcer, NOS	1 (2%)		
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, chronic focal			2 (4%)
Erosion			1 (2%)
#Forestomach	(48)	(19)	(50)
Ulcer, NOS	1 (2%)		2 (4%)
Ulcer, acute	1 (2%)	2 (11%)	
Inflammation, acute focal		1 (5%)	
Inflammation, acute/chronic		1 (5%)	
Ulcer, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Erosion			1 (2%)
Hyperplasia, epithelial			4 (8%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Duodenum	(45)	(16)	(46)
Diverticulum		1 (6%)	
Inflammation, chronic focal			1 (2%)
Metaplasia, osseous			1 (2%)
#Cecum	(45)	(14)	(46)
Metaplasia, squamous		1 (7%)	
URINARY SYSTEM			
#Kidney	(48)	(22)	(49)
Inflammation, acute focal	1 (2%)		
Inflammation, chronic	1 (2%)	1 (5%)	
Nephropathy	44 (92%)	17 (77%)	38 (78%)
Pigmentation, NOS			4 (8%)
#Urinary bladder	(47)	(14)	(48)
Hemorrhage	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(50)
Ectopia			1 (2%)
#Anterior pituitary	(49)	(49)	(50)
Cyst, NOS	2 (4%)	3 (6%)	
Hemorrhage	1 (2%)	1 (2%)	2 (4%)
Necrosis, NOS		1 (2%)	
Necrosis, diffuse	1 (2%)		
Hyperplasia, NOS	9 (18%)	8 (16%)	2 (4%)
Hyperplasia, focal			2 (4%)
Angiectasis		2 (4%)	1 (2%)
#Adrenal cortex	(50)	(15)	(50)
Cyst, NOS	1 (2%)		
Cytoplasmic vacuolization	3 (6%)		2 (4%)
Focal cellular change			1 (2%)
Hyperplasia, NOS			1 (2%)
#Adrenal medulla	(50)	(15)	(50)
Hyperplasia, NOS	15 (30%)	1 (7%)	14 (28%)
#Thyroid	(49)	(16)	(49)
Embryonal duct cyst	1 (2%)	2 (13%)	2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Pigmentation, NOS	1 (2%)		
Hyperplasia, C-cell	5 (10%)	1 (6%)	9 (18%)
#Parathyroid	(39)	(7)	(40)
Hyperplasia, NOS		1 (14%)	
#Pancreatic islets	(47)	(14)	(50)
Hyperplasia, NOS	2 (4%)		4 (8%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Cyst, NOS	1 (2%)		
Hemorrhagic cyst			1 (2%)
Inflammation, acute	8 (16%)	2 (4%)	3 (6%)
Inflammation, active chronic	1 (2%)		2 (4%)
Inflammation, chronic	4 (8%)		11 (22%)
Hyperplasia, NOS		2 (4%)	

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(48)	(14)	(48)
Inflammation, acute		1 (7%)	1 (2%)
Inflammation, chronic	2 (4%)		2 (4%)
#Testis	(49)	(42)	(49)
Atrophy, NOS	30 (61%)	24 (57%)	26 (53%)
Hyperplasia, interstitial cell	4 (8%)		7 (14%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(14)	(50)
Status spongiosis		1 (7%)	
#Cerebellum	(50)	(14)	(50)
Inflammation, chronic focal			1 (2%)
*Optic nerve	(50)	(50)	(50)
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage			6 (12%)
*Eye/anterior chamber	(50)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	
*Eye/sclera	(50)	(50)	(50)
Metaplasia, osseous	12 (24%)	24 (48%)	11 (22%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
*Eye/iris	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	1 (2%)	3 (6%)	24 (48%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)	3 (6%)	23 (46%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, acute focal			1 (2%)
*Harderian gland	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, chronic			5 (10%)
Inflammation, chronic focal	2 (4%)		7 (14%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteoporosis		1 (2%)	
*Maxilla	(50)	(50)	(50)
Fibrous dysplasia			1 (2%)
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Fibrosis, multifocal	1 (2%)		
Foreign material, NOS	1 (2%)		
Hyperplasia, mesothelial			1 (2%)

TABLE A4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Epicardium	(50)	(50)	(50)
Inflammation, acute diffuse			1 (2%)
Inflammation, acute necrotizing	1 (2%)		
Inflammation, chronic focal	2 (4%)		1 (2%)
Hyperplasia, focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	2 (4%)		1 (2%)
Necrosis, fat	3 (6%)	4 (8%)	4 (8%)
ALL OTHER SYSTEMS			
Craniobuccal pouch			
Cyst, NOS		2	1
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		1 (2%)
*Skin	(50)	(50)	(50)
Neurilemoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		1 (2%)
Myxoma			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(46)	(49)
Adenomatous polyp, NOS		1 (2%)	
#Lung	(49)	(49)	(50)
Cortical carcinoma, metastatic	1 (2%)		
Pheochromocytoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	8 (16%)	7 (14%)	5 (10%)
#Salivary gland	(47)	(48)	(49)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
None			
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(47)	(49)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	28 (56%)	17 (36%)	9 (18%)
#Adrenal	(48)	(46)	(50)
Cortical adenoma			1 (2%)
Cortical carcinoma	1 (2%)		
#Adrenal medulla	(48)	(46)	(50)
Pheochromocytoma	1 (2%)	3 (7%)	2 (4%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(49)	(46)	(50)
C-cell adenoma	2 (4%)	2 (4%)	1 (2%)
C-cell carcinoma	1 (2%)	1 (2%)	
#Pancreatic islets	(47)	(44)	(50)
Islet cell carcinoma			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	1 (2%)	
Adenocarcinoma, NOS	2 (4%)		
Fibroadenoma	24 (48%)	11 (22%)	11 (22%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	2 (4%)	
#Uterus	(49)	(46)	(50)
Leiomyoma			1 (2%)
Endometrial stromal polyp	12 (24%)	9 (20%)	6 (12%)
Endometrial stromal sarcoma		1 (2%)	1 (2%)
Mesothelioma, NOS		1 (2%)	
#Ovary	(47)	(45)	(50)
Gonadal stromal tumor		1 (2%)	
#Mesovarium	(47)	(45)	(50)
Mesothelioma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(47)	(50)
Astrocytoma	1 (2%)		
#Brain	(50)	(47)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Endometrial stromal sarcoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	11	11	17
Moribund sacrifice	3	5	3
Terminal sacrifice	35	17	17
Dosing accident	1	17	13

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	46	29	26
Total primary tumors	87	58	43
Total animals with benign tumors	43	27	22
Total benign tumors	72	46	33
Total animals with malignant tumors	14	9	8
Total malignant tumors	15	9	10
Total animals with secondary tumors##	2	1	1
Total secondary tumors	2	1	1
Total animals with tumors uncertain--benign or malignant		2	
Total uncertain tumors		3	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 BENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 90	C 60	C 64	C 87	C 63	C 86	C 68	C 52	C 93	C 98	C 81	C 97	C 59	C 61	C 51	C 53	C 54	C 55	C 56	C 57	C 58	C 62	C 65	C 66	C 67
WEEKS ON STUDY	076	082	086	089	091	095	096	099	099	099	101	102	103	103	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Neurilemoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Fibroma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma, metastatic																									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	−	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X																	
Adenoma, NOS	X	X		X	X	X				X	X			X		X	X		X	X	X	X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																									X
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma				X				X																	
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	−	−	+	−	−	+	+	−	+	+	−	−	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS					X												X								
Fibroadenoma				X		X	X			X				X		X		X	X	X			X	X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp			X	X													X						X		
Ovary	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic								X																	
Astrocytoma																		X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, malignant														X											
Leukemia, mononuclear cell				X		X			X				X					X			X				

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	C 6 9	C 7 0	C 7 1	C 7 2	C 7 3	C 7 4	C 7 5	C 7 6	C 7 7	C 7 8	C 7 9	C 8 0	C 8 2	C 8 3	C 8 4	C 8 5	C 8 8	C 8 9	C 9 1	C 9 2	C 9 4	C 9 5	C 9 6	C 9 9	1 0 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma															X											1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical carcinoma, metastatic																										1
Trachea	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Liver	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bile duct	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS	X				X	X	X		X	X	X		X		X		X			X		X	X		X	28
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical carcinoma																										1
Pheochromocytoma						X																				1
Thyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																										2
C-cell carcinoma										X																1
Parathyroid	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS	X						X																			2
Adenocarcinoma, NOS																										2
Fibroadenoma		X	X	X							X			X		X	X	X	X	X		X		X	24
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp				X	X				X				X			X	X					X	X			12
Ovary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Astrocytoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, malignant																										1
Leukemia, mononuclear cell												X										X				8

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: LOW DOSE

ANIMAL NUMBER	C55	C94	C63	C84	C93	C56	C65	C97	C60	C69	C61	C76	C89	C54	C82	C57	C62	C78	C53	C59	C64	C51	100	C91	C87
WEEKS ON STUDY	000	009	016	116	116	223	233	233	244	400	444	444	444	449	500	522	533	533	544	566	688	711	781	811	833
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thymus	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+
Esophagus	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Stomach	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Small intestine	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Large intestine	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Urinary bladder	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Adenoma, NOS														X								X		X	
Adrenal	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Pheochromocytoma																									
Thyroid	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	+	−	−	−	+	+	+	+	+	+	−	−	+	−	+	−	+	+	+	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Fibroadenoma											X											X		X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp															X						X				X
Endometrial stromal sarcoma																					X				
Mesothelioma, NOS																									
Ovary	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Gonadal stromal tumor																									
Mesothelioma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Endometrial stromal sarcoma, metastatic																					X				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																						X			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	C 9 9	C 7 2	C 7 0	C 6 7	C 6 8	C 8 0	C 9 5	C 5 2	C 5 8	C 6 6	C 7 1	C 7 3	C 7 4	C 7 5	C 7 7	C 7 9	C 8 1	C 8 3	C 8 5	C 8 6	C 8 8	C 9 0	C 9 2	C 9 6	C 9 8	TOTAL:
WEEKS ON STUDY	0 8 8	0 8 9	0 9 4	0 9 9	0 9 9	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenomatous polyp, NOS																		X								1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Esophagus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	43
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X	X	X	X			X		X			X		X	X	X	X	X						X	X	17
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pheochromocytoma					X							X											X			3
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell adenoma											X												X			2
C-cell carcinoma												X														1
Parathyroid	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS						X																				1
Fibroadenoma			X			X	X					X			X						X		X		X	11
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																	X							X		2
Uterus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Endometrial stromal polyp				X										X				X			X	X	X			9
Endometrial stromal sarcoma																										1
Mesothelioma, NOS	X																									1
Ovary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Gonadal stromal tumor														X												1
Mesothelioma, NOS	X																									1
NERVOUS SYSTEM																										
Brain	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Endometrial stromal sarcoma, meta																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell			X	X	X					X				X						X						7

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: HIGH DOSE

ANIMAL NUMBER	C 5 5	C 6 7	C 9 7	C 8 8	C 5 6	C 6 3	C 6 6	C 6 8	C 6 0	C 6 4	C 7 3	C 9 6	C 7 6	C 8 5	C 8 1	C 8 9	C 9 9	1 0 0	C 9 1	C 7 7	C 7 8	C 6 1	C 8 6	C 5 4	C 9 3
WEEKS ON STUDY	0 1 5	0 1 6	0 1 7	0 2 1	0 2 3	0 2 3	0 2 3	0 2 4	0 2 8	0 4 1	0 4 5	0 4 5	0 4 7	0 4 8	0 4 9	0 5 1	0 5 4	0 5 4	0 5 6	0 5 9	0 8 5	0 8 8	0 9 3	0 9 5	0 9 5
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Myxoma																				X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	+	–	–	+	+	+	+	–	–	+	+	–	+	–	–	–	+	+	–	+	–	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibroadenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp															X										X
Endometrial stromal sarcoma																X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrous histiocytoma, malignant																						X			
Leukemia, mononuclear cell																					X		X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	C 7 2	C 5 7	C 8 0	C 6 2	C 9 5	C 5 9	C 8 4	C 7 9	C 5 1	C 5 2	C 5 3	C 5 8	C 6 5	C 6 9	C 7 0	C 7 1	C 7 4	C 7 5	C 8 2	C 8 3	C 8 7	C 9 0	C 9 2	C 9 4	C 9 8	TOTAL:
WEEKS ON STUDY	0 9 7	0 9 9	0 9 9	1 0 0	1 0 1	1 0 2	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma										X																1
Myxoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS												X														1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X				X					X		X				X							X		X	9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																						X				1
Pheochromocytoma								X				X														2
Pheochromocytoma, malignant												X														1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma															X											1
Parathyroid	−	−	−	+	+	+	−	+	+	+	−	+	−	−	+	−	−	+	+	+	−	−	+	−	+	27
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma															X											1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma	X				X	X		X	X	X	X		X									X		X	X	11
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma			X																							1
Endometrial stromal polyp				X			X									X						X				6
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, malignant																										1
Leukemia, mononuclear cell			X	X								X														5

* Animals necropsied

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

	Vehicle Control	200 mg/kg	400 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	8/50 (16%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	19.1%	30.0%	19.7%
Terminal Rates (c)	4/36 (11%)	3/18 (17%)	1/17 (6%)
Week of First Observation	89	71	85
Life Table Tests (d)	P=0.383	P=0.208	P=0.503
Incidental Tumor Tests (d)	P=0.390N	P=0.343	P=0.482N
Cochran-Armitage Trend Test (d)	P=0.231N		
Fisher Exact Test (d)		P=0.500N	P=0.277N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	28/50 (56%)	17/47 (36%)	9/49 (18%)
Adjusted Rates (b)	63.0%	64.0%	39.5%
Terminal Rates (c)	20/36 (56%)	9/18 (50%)	5/17 (29%)
Week of First Observation	76	49	48
Life Table Tests (d)	P=0.141N	P=0.310	P=0.109N
Incidental Tumor Tests (d)	P=0.009N	P=0.429N	P=0.008N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.040N	P<0.001N
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	29/50 (58%)	17/47 (36%)	9/49 (18%)
Adjusted Rates (b)	63.8%	64.0%	39.5%
Terminal Rates (c)	20/36 (56%)	9/18 (50%)	5/17 (29%)
Week of First Observation	76	49	48
Life Table Tests (d)	P=0.113N	P=0.359	P=0.088N
Incidental Tumor Tests (d)	P=0.004N	P=0.364N	P=0.004N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.026N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	1/48 (2%)	3/46 (7%)	(e) 2/50 (4%)
Adjusted Rates (b)	2.9%	15.2%	11.1%
Terminal Rates (c)	1/35 (3%)	2/18 (11%)	1/17 (6%)
Week of First Observation	104	99	103
Life Table Tests (d)	P=0.157	P=0.110	P=0.258
Incidental Tumor Tests (d)	P=0.263	P=0.122	P=0.373
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.292	P=0.515
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	3/46 (7%)	1/50 (2%)
Adjusted Rates (b)	7.1%	16.7%	5.9%
Terminal Rates (c)	1/35 (3%)	3/18 (17%)	1/17 (6%)
Week of First Observation	89	104	104
Life Table Tests (d)	P=0.536N	P=0.338	P=0.548N
Incidental Tumor Tests (d)	P=0.487N	P=0.378	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.234N		
Fisher Exact Test (d)		P=0.631	P=0.301N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	24/50 (48%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (b)	58.0%	43.6%	51.7%
Terminal Rates (c)	19/36 (53%)	5/18 (28%)	7/17 (41%)
Week of First Observation	89	44	97
Life Table Tests (d)	P=0.412N	P=0.441N	P=0.500N
Incidental Tumor Tests (d)	P=0.104N	P=0.186N	P=0.227N
Cochran-Armitage Trend Test (d)	P=0.093N		
Fisher Exact Test (d)		P=0.006N	P=0.006N

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

	Vehicle Control	200 mg/kg	400 mg/kg
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	26/50 (52%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (b)	62.9%	43.6%	51.7%
Terminal Rates (c)	21/36 (58%)	5/18 (28%)	7/17 (41%)
Week of First Observation	89	44	97
Life Table Tests (d)	P=0.298N	P=0.333N	P=0.386N
Incidental Tumor Tests (d)	P=0.056N	P=0.114N	P=0.146N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.002N	P=0.002N
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.3%	5.0%	0.0%
Terminal Rates (c)	3/36 (8%)	0/18 (0%)	0/17 (0%)
Week of First Observation	91	102	
Life Table Tests (d)	P=0.108N	P=0.434N	P=0.183N
Incidental Tumor Tests (d)	P=0.079N	P=0.368N	P=0.194N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.181N	P=0.059N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	28/50 (56%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (b)	66.2%	43.6%	51.7%
Terminal Rates (c)	22/36 (61%)	5/18 (28%)	7/17 (41%)
Week of First Observation	89	44	97
Life Table Tests (d)	P=0.200N	P=0.242N	P=0.278N
Incidental Tumor Tests (d)	P=0.027N	P=0.057N	P=0.089N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	12/49 (24%)	9/46 (20%)	6/50 (12%)
Adjusted Rates (b)	30.8%	37.7%	25.1%
Terminal Rates (c)	10/36 (28%)	5/18 (28%)	2/17 (12%)
Week of First Observation	86	50	49
Life Table Tests (d)	P=0.512	P=0.246	P=0.587N
Incidental Tumor Tests (d)	P=0.282N	P=0.510	P=0.334N
Cochran-Armitage Trend Test (d)	P=0.071N		
Fisher Exact Test (d)		P=0.371N	P=0.088N
All Sites: Benign Tumors			
Overall Rates (a)	43/50 (86%)	27/50 (54%)	22/50 (44%)
Adjusted Rates (b)	91.4%	84.1%	77.9%
Terminal Rates (c)	32/36 (89%)	13/18 (72%)	11/17 (65%)
Week of First Observation	76	44	48
Life Table Tests (d)	P=0.468	P=0.162	P=0.549
Incidental Tumor Tests (d)	P=0.010N	P=0.253N	P=0.018N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
All Sites: Malignant Tumors			
Overall Rates (a)	14/50 (28%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	31.9%	36.9%	29.4%
Terminal Rates (c)	7/36 (19%)	4/18 (22%)	2/17 (12%)
Week of First Observation	89	68	51
Life Table Tests (d)	P=0.448	P=0.367	P=0.527
Incidental Tumor Tests (d)	P=0.210N	P=0.548N	P=0.268N
Cochran-Armitage Trend Test (d)	P=0.087N		
Fisher Exact Test (d)		P=0.171N	P=0.114N

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

	Vehicle Control	200 mg/kg	400 mg/kg
All Sites: All Tumors			
Overall Rates (a)	46/50 (92%)	29/50 (58%)	26/50 (52%)
Adjusted Rates (b)	93.8%	90.4%	80.7%
Terminal Rates (c)	33/36 (92%)	15/18 (83%)	11/17 (65%)
Week of First Observation	76	44	48
Life Table Tests (d)	P=0.285	P=0.133	P=0.347
Incidental Tumor Tests (d)	P=0.013N	P=0.276N	P=0.013N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N

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

TABLE B4. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 645/1,654 (39.0%)	(c) 49/1,654 (3.0%)	(b,c) 692/1,654 (41.8%)
SD (d)	10.37%	2.92%	10.52%
Range (e)			
High	32/49	5/47	33/49
Low	9/50	0/50	11/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes 72 chromophobe adenomas
(c) Includes eight adenocarcinomas, NOS, and four chromophobe carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		2 (4%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(46)	(49)
Inflammation, acute	2 (4%)		
#Accessory sinus	(50)	(46)	(49)
Inflammation, acute		1 (2%)	
*Larynx	(50)	(50)	(50)
Hemorrhage		4 (8%)	3 (6%)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Trachea	(49)	(47)	(50)
Hemorrhage		1 (2%)	2 (4%)
Fibrosis			1 (2%)
#Lung	(49)	(49)	(50)
Vegetable foreign body		1 (2%)	
Congestion, NOS	1 (2%)	1 (2%)	5 (10%)
Edema, NOS		1 (2%)	
Hemorrhage		5 (10%)	10 (20%)
Pneumonia, aspiration		1 (2%)	
Bronchopneumonia, acute			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Pneumonia, interstitial chronic	1 (2%)		1 (2%)
Inflammation, chronic focal	2 (4%)		
Inflammation, granulomatous focal		1 (2%)	
Scar	1 (2%)		
Necrosis, caseous	1 (2%)		
Proteinosis, alveolar	1 (2%)		
Foreign material, NOS	1 (2%)	18 (37%)	12 (24%)
Pigmentation, NOS		1 (2%)	
Hyperplasia, adenomatous	7 (14%)	1 (2%)	2 (4%)
Histiocytosis	43 (88%)	24 (49%)	26 (52%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(48)	(50)
Hyperplasia, NOS		1 (2%)	1 (2%)
Hyperplasia, reticulum cell	4 (8%)		
#Spleen	(48)	(46)	(50)
Congestion, NOS			1 (2%)
Fibrosis, multifocal			1 (2%)
Necrosis, diffuse			1 (2%)
Infarct, NOS	1 (2%)		
Pigmentation, NOS	28 (58%)	17 (37%)	34 (68%)
Hematopoiesis	3 (6%)	2 (4%)	2 (4%)
#Mandibular lymph node	(48)	(46)	(50)
Cyst, NOS			1 (2%)
Hemorrhage		1 (2%)	
Abscess, NOS		1 (2%)	
Pigmentation, NOS			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Mediastinal lymph node	(48)	(46)	(50)
Hemorrhage	2 (4%)	2 (4%)	
Plasmacytosis	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(48)	(46)	(50)
Edema, NOS			1 (2%)
Hemorrhage	3 (6%)	2 (4%)	
Histiocytosis			1 (2%)
#Lung	(49)	(49)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Liver	(48)	(49)	(50)
Leukocytosis, NOS			1 (2%)
Hematopoiesis	1 (2%)		2 (4%)
#Adrenal cortex	(48)	(46)	(50)
Hematopoiesis	1 (2%)		
#Thymus	(44)	(44)	(47)
Embryonal duct cyst			1 (2%)
Congestion, NOS			2 (4%)
Hemorrhage			3 (6%)
Atrophy, NOS			1 (2%)
CIRCULATORY SYSTEM			
#Brain	(50)	(47)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
*Nasal cavity	(50)	(46)	(49)
Thrombosis, NOS	1 (2%)		
#Lung	(49)	(49)	(50)
Thrombosis, NOS		1 (2%)	
#Heart	(49)	(49)	(50)
Inflammation, acute focal	1 (2%)		
Inflammation, chronic	6 (12%)	9 (18%)	11 (22%)
Fibrosis	1 (2%)	2 (4%)	
Fibrosis, focal	4 (8%)		
Fibrosis, multifocal	24 (49%)	3 (6%)	14 (28%)
#Heart/atrium	(49)	(49)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
#Myocardium	(49)	(49)	(50)
Inflammation, chronic			1 (2%)
#Cardiac valve	(49)	(49)	(50)
Inflammation, chronic focal	1 (2%)		
Endocardiosis			1 (2%)
*Coronary artery	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic	1 (2%)		
Degeneration, hyaline			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization			1 (2%)
*Renal artery	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
DIGESTIVE SYSTEM			
*Alveolus dentalis	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
#Salivary gland	(47)	(48)	(49)
Inflammation, acute focal	1 (2%)		
Fibrosis, diffuse			1 (2%)
#Parotid gland	(47)	(48)	(49)
Inflammation, chronic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(48)	(49)	(50)
Congestion, acute passive			1 (2%)
Congestion, chronic passive			1 (2%)
Hemorrhage	1 (2%)		
Inflammation, acute focal	1 (2%)	2 (4%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic focal	12 (25%)	2 (4%)	9 (18%)
Scar	1 (2%)		
Peliosis hepatis	3 (6%)		2 (4%)
Necrosis, focal	4 (8%)		
Mitotic alteration			1 (2%)
Cytoplasmic vacuolization	2 (4%)	1 (2%)	1 (2%)
Basophilic cyto change	27 (56%)	21 (43%)	21 (42%)
Focal cellular change	2 (4%)		1 (2%)
Cytologic alteration, NOS	1 (2%)	2 (4%)	4 (8%)
Hyperplastic nodule			1 (2%)
#Liver/centrilobular	(48)	(49)	(50)
Congestion, chronic			1 (2%)
Necrosis, diffuse		2 (4%)	1 (2%)
Cytoplasmic vacuolization		2 (4%)	2 (4%)
#Liver/hepatocytes	(48)	(49)	(50)
Hyperplasia, focal	1 (2%)		
#Bile duct	(48)	(49)	(50)
Hyperplasia, NOS	19 (40%)	9 (18%)	16 (32%)
#Pancreas	(47)	(44)	(50)
Ectopia		1 (2%)	
Cyst, NOS	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	3 (6%)		
Inflammation, chronic diffuse	1 (2%)		
Necrosis, focal	1 (2%)		
Atrophy, focal			1 (2%)
#Pancreatic acinus	(47)	(44)	(50)
Atrophy, NOS		2 (5%)	
Atrophy, focal	11 (23%)	1 (2%)	7 (14%)
#Esophagus	(49)	(46)	(49)
Hemorrhage	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Pigmentation, NOS		1 (2%)	
#Esophageal adventitia	(49)	(46)	(49)
Fibrosis			1 (2%)
#Glandular stomach	(48)	(45)	(50)
Cyst, NOS	1 (2%)		
Ulcer, NOS	1 (2%)		
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
#Gastric muscularis	(48)	(45)	(50)
Degeneration, hyaline	1 (2%)		
#Forestomach	(48)	(45)	(50)
Ulcer, NOS	1 (2%)		
Ulcer, acute	1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(48)	(46)	(50)
Mineralization	2 (4%)	1 (2%)	3 (6%)
Cyst, NOS		1 (2%)	
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Nephropathy	34 (71%)	16 (35%)	20 (40%)
Necrosis, focal		1 (2%)	
Pigmentation, NOS	1 (2%)	1 (2%)	1 (2%)
#Urinary bladder	(46)	(46)	(49)
Inflammation, chronic focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(47)	(49)
Cyst, NOS	8 (16%)	5 (11%)	7 (14%)
Hemorrhage	1 (2%)		
Granuloma, NOS		1 (2%)	
Necrosis, NOS	1 (2%)		
Hyperplasia, NOS	5 (10%)	3 (6%)	6 (12%)
Angiectasis	8 (16%)	7 (15%)	10 (20%)
#Adrenal	(48)	(46)	(50)
Hypertrophy, focal	1 (2%)	1 (2%)	
#Adrenal cortex	(48)	(46)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Necrosis, NOS	1 (2%)		
Necrosis, focal		1 (2%)	
Cytoplasmic vacuolization	3 (6%)	3 (7%)	2 (4%)
Atrophy, NOS	1 (2%)		
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)
Angiectasis	1 (2%)		2 (4%)
#Adrenal medulla	(48)	(46)	(50)
Hyperplasia, NOS	5 (10%)	4 (9%)	2 (4%)
Hyperplasia, focal	1 (2%)		1 (2%)
#Thyroid	(49)	(46)	(50)
Embryonal duct cyst	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS		1 (2%)	
Hyperplasia, C-cell	11 (22%)	3 (7%)	6 (12%)
#Parathyroid	(38)	(37)	(27)
Hyperplasia, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	7 (14%)	7 (14%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	2 (4%)		
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		2 (4%)
Inflammation, acute	1 (2%)	1 (2%)	5 (10%)
Inflammation, acute suppurative		2 (4%)	
Abscess, NOS			3 (6%)
Inflammation, active chronic			2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, NOS		3 (6%)	
*Vagina	(50)	(50)	(50)
Inflammation, acute	2 (4%)		
Inflammation, acute diffuse	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(49)	(46)	(50)
Dilatation, NOS			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)	5 (11%)	1 (2%)
Necrosis, NOS			1 (2%)
#Cervix/uteri	(49)	(46)	(50)
Cyst, NOS		1 (2%)	
#Uterus/endometrium	(49)	(46)	(50)
Inflammation, acute		1 (2%)	
Hyperplasia, cystic	6 (12%)	6 (13%)	9 (18%)
#Ovary	(47)	(45)	(50)
Cyst, NOS	4 (9%)	4 (9%)	4 (8%)
NERVOUS SYSTEM			
*Choroid plexus	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(50)	(47)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Infarct, NOS			1 (2%)
#Cerebellum	(50)	(47)	(50)
Hemorrhage			1 (2%)
Inflammation, acute suppurative			1 (2%)
*Spinal cord	(50)	(50)	(50)
Hemorrhage			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Synechia, anterior		1 (2%)	
*Eye/sclera	(50)	(50)	(50)
Metaplasia, osseous	6 (12%)	4 (8%)	2 (4%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	1 (2%)	3 (6%)	20 (40%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)	2 (4%)	16 (32%)
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic		5 (10%)	2 (4%)
Inflammation, chronic focal	9 (18%)		8 (16%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Hyperostosis			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Fibrosis	1 (2%)		
*Pleura	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Inflammation, acute	1 (2%)		
Granuloma, NOS	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Epicardium	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic	3 (6%)		2 (4%)
Inflammation, granulomatous		1 (2%)	
Granuloma, NOS		2 (4%)	
Necrosis, NOS		1 (2%)	
Necrosis, coagulative			1 (2%)
Necrosis, fat	4 (8%)	5 (10%)	3 (6%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute suppurative		1 (2%)	
Adipose tissue			
Inflammation, chronic			2
Necrosis, fat	2		1
Craniobuccal pouch			
Cyst, NOS			1
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma	2 (4%)	2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	2 (4%)	1 (2%)	3 (6%)
Alveolar/bronchiolar adenoma	8 (16%)	6 (13%)	13 (26%)
Alveolar/bronchiolar carcinoma	3 (6%)	1 (2%)	4 (8%)
Sarcoma, NOS			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	3 (6%)		1 (2%)
Malignant lymphoma, histiocytic type		2 (4%)	
Malignant lymphoma, mixed type	3 (6%)	2 (4%)	3 (6%)
#Spleen	(47)	(18)	(47)
Malignant lymphoma, mixed type	1 (2%)	1 (6%)	
#Mediastinal lymph node	(47)	(22)	(48)
Malignant lymphoma, lymphocytic type		1 (5%)	
#Mesenteric lymph node	(47)	(22)	(48)
Malignant lymphoma, lymphocytic type		1 (5%)	
#Small intestine	(44)	(14)	(45)
Malignant lymphoma, NOS	1 (2%)		
#Peyer's patch	(44)	(14)	(45)
Malignant lymphoma, mixed type		1 (7%)	
#Duodenum	(44)	(14)	(45)
Malignant lymphoma, mixed type			1 (2%)
#Thymus	(40)	(14)	(44)
Thymoma, benign	2 (5%)		
Malignant lymphoma, histiocytic type	1 (3%)		
CIRCULATORY SYSTEM			
*Skin	(50)	(50)	(50)
Hemangioma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			2 (4%)
Hemangiosarcoma	1 (2%)		
#Heart	(50)	(16)	(50)
Sarcoma, NOS			1 (2%)
Hemangiosarcoma			1 (2%)
#Liver	(50)	(48)	(50)
Hemangiosarcoma			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS	1 (2%)		
#Liver	(50)	(48)	(50)
Hepatocellular adenoma	6 (12%)	8 (17%)	7 (14%)
Hepatocellular carcinoma	6 (12%)	9 (19%)	10 (20%)
#Pancreas	(47)	(15)	(47)
Adenocarcinoma, NOS		1 (7%)	
#Esophagus	(48)	(15)	(50)
Sarcoma, NOS			1 (2%)
#Stomach	(44)	(15)	(47)
Adenocarcinoma, NOS, metastatic		1 (7%)	
#Forestomach	(44)	(15)	(47)
Papilloma, NOS		1 (7%)	
#Small intestine	(44)	(14)	(45)
Adenomatous polyp, NOS	1 (2%)		
#Jejunum	(44)	(14)	(45)
Adenocarcinoma, NOS		1 (7%)	
URINARY SYSTEM			
#Kidney	(50)	(48)	(49)
Adenocarcinoma, NOS, metastatic		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(16)	(49)
Adenoma, NOS			2 (4%)
#Adrenal	(48)	(44)	(48)
Cortical adenoma			3 (6%)
#Adrenal/capsule	(48)	(44)	(48)
Adenoma, NOS		1 (2%)	1 (2%)
#Adrenal medulla	(48)	(44)	(48)
Pheochromocytoma	2 (4%)		2 (4%)
Ganglioneuroma			1 (2%)
#Thyroid	(48)	(16)	(50)
Follicular cell adenoma	1 (2%)		2 (4%)
Follicular cell carcinoma			1 (2%)
#Pancreatic islets	(47)	(15)	(47)
Islet cell adenoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
#Testis	(49)	(16)	(50)
Interstitial cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	8 (16%)	3 (6%)	2 (4%)

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

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Rib	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Sarcoma, NOS			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
*Abdominal cavity	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	11	8	8
Moribund sacrifice	1	3	1
Terminal sacrifice	34	33	35
Dosing accident	3	6	6
Accidentally killed, nda	1		
TUMOR SUMMARY			
Total animals with primary tumors**	34	27	34
Total primary tumors	53	41	64
Total animals with benign tumors	24	16	26
Total benign tumors	31	19	37
Total animals with malignant tumors	22	17	21
Total malignant tumors	22	22	27
Total animals with secondary tumors##	2	3	3
Total secondary tumors	2	8	3

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 BENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C36	C30	C40	C22	C35	C09	C08	C27	C01	C03	C19	C04	C31	C47	C21	C50	C02	C05	C06	C07	C10	C11	C12	C13	C14
WEEKS ON STUDY	009	016	021	039	048	053	054	057	061	067	079	084	098	099	102	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Fibrosarcoma							X	X																	
Hemangiosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																			X						
Alveolar/bronchiolar adenoma												X													X
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	+	−	+	−	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Thymoma, benign																									
Malignant lymphoma, histiocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X								X
Hepatocellular carcinoma															X				X				X		X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	+	+	N	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	−	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	−	+	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Malignant lymphoma, NOS																									
Large intestine	−	+	−	−	+	+	−	+	+	−	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X											
Thyroid	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	−	+	−	+	−	−	+	+	−	+	+	−	−	-	−	+	+	+	+	−	+	+	+	+	+
Pancreatic islets	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N
Testis	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																	X								
Prostate	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS					X					X			X					X		X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type									X		X			X											
Malignant lymphoma, mixed type													X												

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	C 1 5	C 1 6	C 1 7	C 1 8	C 2 0	C 2 3	C 2 4	C 2 5	C 2 6	C 2 8	C 2 9	C 3 2	C 3 3	C 3 4	C 3 7	C 3 8	C 3 9	C 4 1	C 4 2	C 4 3	C 4 4	C 4 5	C 4 6	C 4 8	C 4 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibrosarcoma																										2
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic			X																							2
Alveolar/bronchiolar adenoma	X											X	X							X		X			X	8
Alveolar/bronchiolar carcinoma															X	X						X				3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type																			X							1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Thymoma, benign						X	X																			2
Malignant lymphoma, histiocytic type													X													1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																X										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma												X							X		X				X	6
Hepatocellular carcinoma			X			X																				6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenomatous polyp, NOS			X																							1
Malignant lymphoma, NOS				X																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Pheochromocytoma															X											2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Parathyroid	+	+	+	−	−	+	+	+	+	−	+	−	−	+	−	+	+	+	−	+	+	+	−	+	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma			X																							1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS															X			X		X						8
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										3
Malignant lymphoma, mixed type									X															X		3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: LOW DOSE

ANIMAL NUMBER	C 0 3	C 4 1	C 2 3	C 2 1	C 2 0	C 3 9	C 4 0	C 3 8	C 4 7	C 2 6	C 0 1	C 0 4	C 1 3	C 2 7	C 3 4	C 1 4	C 0 7	C 0 2	C 0 5	C 0 6	C 0 8	C 0 9	C 1 0	C 1 1	C 1 2
WEEKS ON STUDY	0 2 6	0 3 6	0 5 3	0 6 6	0 6 8	0 6 9	0 7 1	0 7 5	0 7 5	0 8 3	0 8 5	0 8 7	0 9 2	0 9 2	0 9 2	0 9 5	0 9 7	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N
Fibrosarcoma												X	X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic				X																					
Hepatocellular carcinoma, metastatic																X									
Alveolar/bronchiolar adenoma																								X	
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	–	–	–	–	+	–	–	–
Malignant lymphoma, lymphocytic type																									
Thymus	+	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma				X						X							X	X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	N	+	N	+	+	+	+	N	N	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Adenocarcinoma, NOS				X																					
Esophagus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	–	–	–	–	–	+	–	–	–
Papilloma, NOS												X													
Adenocarcinoma, NOS, metastatic				X																					
Small intestine	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	–	–	+	–	–	–	–	–	–	–
Adenocarcinoma, NOS																		X							
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic				X																					
Urinary bladder	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Adrenal	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Parathyroid	–	–	–	+	–	+	–	+	–	–	–	–	–	+	+	+	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
Prostate	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																X									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic				X																					
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic				X																					
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, histiocytic type														X		X									
Malignant lymphoma, mixed type						X									X										

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	C 1 1 5	C 1 1 6	C 1 1 7	C 1 1 8	C 1 1 9	C 2 2 2	C 2 2 4	C 2 2 5	C 2 2 8	C 2 2 9	C 3 3 0	C 3 3 1	C 3 3 2	C 3 3 3	C 3 3 5	C 3 3 6	C 3 3 7	C 4 2 2	C 4 3 3	C 4 4 4	C 4 4 5	C 4 4 6	C 4 4 8	C 4 4 9	C 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	48
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma	X											X	X				X								X	6
Alveolar/bronchiolar carcinoma												X														1
Fibrosarcoma, metastatic																										1
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Spleen	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	18
Malignant lymphoma, mixed type																							X			1
Lymph nodes	+	+	−	−	−	+	−	−	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	+	22
Malignant lymphoma, lymphocytic type		X				X																				2
Thymus	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	48
Hepatocellular adenoma						X		X			X			X	X	X							X			8
Hepatocellular carcinoma		X	X			X												X				X				9
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	N	+	+	N	+	*50
Pancreas	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	15
Adenocarcinoma, NOS																										1
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	15
Stomach	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	15
Papilloma, NOS																										1
Adenocarcinoma, NOS, metastatic																										1
Small intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	14
Adenocarcinoma, NOS																										1
Malignant lymphoma, mixed type																						X				1
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	12
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	48
Adenocarcinoma, NOS, metastatic																										1
Urinary bladder	−	+	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	17
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	44
Adenoma, NOS														X												1
Thyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	16
Prostate	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																		X							X	3
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type																										2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: HIGH DOSE

ANIMAL NUMBER	C 0 4	C 1 0	C 1 4	C 2 4	C 2 7	C 2 2	C 0 5	C 3 1	C 4 9	C 2 9	C 0 1	C 3 4	C 4 1	C 1 6	C 3 6	C 0 2	C 0 3	C 0 6	C 0 7	C 0 8	C 0 9	C 1 1	C 1 2	C 1 3	C 1 5
WEEKS ON STUDY	0 0 7	0 0 8	0 4 3	0 5 6	0 5 7	0 6 5	0 7 9	0 8 4	0 8 5	0 9 4	0 9 5	0 9 5	0 9 7	0 9 9	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																							X		
Alveolar/bronchiolar adenoma				X				X				X		X		X		X					X		X
Alveolar/bronchiolar carcinoma																	X								
Sarcoma, NOS										X															
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X															
Hemangiosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X				X	X		
Hepatocellular carcinoma										X			X	X	X	X							X		
Hemangiosarcoma					X																				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	N	+	+	N	+	N	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS										X															
Stomach	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Small intestine	+	–	+	+	+	+	+	–	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma																		X							
Pheochromocytoma																							X		
Ganglioneuroma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							X		
Follicular cell carcinoma																									
Parathyroid	+	–	–	–	–	+	+	+	+	–	–	–	+	–	–	–	+	–	–	+	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X														
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type														X											
Malignant lymphoma, mixed type								X														X			

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	C 1 7	C 1 8	C 1 9	C 2 0	C 2 1	C 2 3	C 2 5	C 2 6	C 2 8	C 3 0	C 3 2	C 3 3	C 3 5	C 3 7	C 3 8	C 3 9	C 4 0	C 4 2	C 4 3	C 4 4	C 4 5	C 4 6	C 4 7	C 4 8	C 5 0	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangioma																						X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																									X	1
Hemangioma								X												X						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																X						X				3
Alveolar/bronchiolar adenoma			X		X													X	X						X	13
Alveolar/bronchiolar carcinoma													X		X						X					4
Sarcoma, NOS																										1
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Thymus	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Hemangiosarcoma			X																							1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X										X		X		X							7
Hepatocellular carcinoma																X		X		X		X				10
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, mixed type				X																						1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS									X				X													2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS										X																1
Cortical adenoma			X																X							3
Pheochromocytoma																								X		2
Ganglioneuroma																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma								X																		2
Follicular cell carcinoma																X										1
Parathyroid	–	–	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	–	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS											X					X										2
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type											X															3

* Animals necropsied

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

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.3%	5.1%	2.9%
Terminal Rates (c)	0/34 (0%)	0/33 (0%)	1/35 (3%)
Week of First Observation	54	87	104
Life Table Tests (d)	P=0.212N	P=0.489N	P=0.294N
Incidental Tumor Tests (d)	P=0.188N	P=0.307N	P=0.353N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	8/50 (16%)	6/48 (13%)	13/50 (26%)
Adjusted Rates (b)	22.6%	19.4%	32.6%
Terminal Rates (c)	7/34 (21%)	6/31 (19%)	9/35 (26%)
Week of First Observation	84	104	56
Life Table Tests (d)	P=0.144	P=0.452N	P=0.194
Incidental Tumor Tests (d)	P=0.155	P=0.394N	P=0.214
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.419N	P=0.163
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	1/48 (2%)	4/50 (8%)
Adjusted Rates (b)	8.8%	3.2%	11.4%
Terminal Rates (c)	3/34 (9%)	1/31 (3%)	4/35 (11%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.426	P=0.338N	P=0.516
Incidental Tumor Tests (d)	P=0.426	P=0.338N	P=0.516
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test (d)		P=0.324N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	6/48 (13%)	17/50 (34%)
Adjusted Rates (b)	28.4%	19.4%	43.0%
Terminal Rates (c)	9/34 (26%)	6/31 (19%)	13/35 (37%)
Week of First Observation	84	104	56
Life Table Tests (d)	P=0.072	P=0.257N	P=0.110
Incidental Tumor Tests (d)	P=0.077	P=0.213N	P=0.121
Cochran-Armitage Trend Test (d)	P=0.059		
Fisher Exact Test (d)		P=0.233N	P=0.088
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	(e,f) 2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.4%		2.7%
Terminal Rates (c)	0/34 (0%)		0/35 (0%)
Week of First Observation	61		99
Life Table Test (d)			P=0.294N
Incidental Tumor Test (d)			P=0.239N
Fisher Exact Test (d)			P=0.309N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	(e,f) 4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	11.2%		10.7%
Terminal Rates (c)	3/34 (9%)		3/35 (9%)
Week of First Observation	98		84
Life Table Test (d)			P=0.625N
Incidental Tumor Test (d)			P=0.574N
Fisher Exact Test (d)			P=0.643N

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

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	(e,f) 8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	23.1%		13.1%
Terminal Rates (c)	5/34 (15%)		3/35 (9%)
Week of First Observation	61		84
Life Table Test (d)			P=0.186N
Incidental Tumor Test (d)			P=0.130N
Fisher Exact Test (d)			P=0.194N
Circulatory System: Hemangioma			
Overall Rates (a)	0/50 (0%)	(e,f) 0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%		8.6%
Terminal Rates (c)	0/34 (0%)		3/35 (9%)
Week of First Observation			104
Life Table Test (d)			P=0.126
Incidental Tumor Test (d)			P=0.126
Fisher Exact Test (d)			P=0.121
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	(e,f) 0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	2.2%		13.4%
Terminal Rates (c)	0/34 (0%)		4/35 (11%)
Week of First Observation	48		57
Life Table Test (d)			P=0.115
Incidental Tumor Test (d)			P=0.075
Fisher Exact Test (d)			P=0.102
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/50 (12%)	8/48 (17%)	7/50 (14%)
Adjusted Rates (b)	17.6%	25.8%	20.0%
Terminal Rates (c)	6/34 (18%)	8/31 (26%)	7/35 (20%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.466	P=0.311	P=0.523
Incidental Tumor Tests (d)	P=0.466	P=0.311	P=0.523
Cochran-Armitage Trend Test (d)	P=0.443		
Fisher Exact Test (d)		P=0.355	P=0.500
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	9/48 (19%)	10/50 (20%)
Adjusted Rates (b)	17.1%	25.3%	25.5%
Terminal Rates (c)	5/34 (15%)	6/31 (19%)	6/35 (17%)
Week of First Observation	102	66	94
Life Table Tests (d)	P=0.203	P=0.245	P=0.230
Incidental Tumor Tests (d)	P=0.259	P=0.238	P=0.298
Cochran-Armitage Trend Test (d)	P=0.175		
Fisher Exact Test (d)		P=0.259	P=0.207
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	11/50 (22%)	16/48 (33%)	16/50 (32%)
Adjusted Rates (b)	31.4%	46.2%	40.9%
Terminal Rates (c)	10/34 (29%)	13/31 (42%)	12/35 (34%)
Week of First Observation	102	66	94
Life Table Tests (d)	P=0.189	P=0.123	P=0.209
Incidental Tumor Tests (d)	P=0.235	P=0.118	P=0.263
Cochran-Armitage Trend Test (d)	P=0.161		
Fisher Exact Test (d)		P=0.152	P=0.184

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

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Gland: Cortical Adenoma			
Overall Rates (a)	0/48 (0%)	0/44 (0%)	3/48 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.6%
Terminal Rates (c)	0/33 (0%)	0/30 (0%)	3/35 (9%)
Week of First Observation			104
Life Table Tests (d)	P=0.044	(g)	P=0.131
Incidental Tumor Tests (d)	P=0.044	(g)	P=0.131
Cochran-Armitage Trend Test (d)	P=0.039		
Fisher Exact Test (d)		(g)	P=0.121
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/48 (2%)	(f) 0/16 (0%)	3/50 (6%)
Adjusted Rates (b)	2.9%		8.6%
Terminal Rates (c)	1/34 (3%)		3/35 (9%)
Week of First Observation	104		104
Life Table Test (d)			P=0.315
Incidental Tumor Test (d)			P=0.315
Fisher Exact Test (d)			P=0.324
Harderian Gland: Adenoma			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	20.7%	8.7%	5.7%
Terminal Rates (c)	5/34 (15%)	2/33 (6%)	2/35 (6%)
Week of First Observation	48	95	104
Life Table Tests (d)	P=0.025N	P=0.115N	P=0.047N
Incidental Tumor Tests (d)	P=0.027N	P=0.169N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.100N	P=0.046N
All Sites: Benign Tumors			
Overall Rates (a)	24/50 (48%)	16/50 (32%)	26/50 (52%)
Adjusted Rates (b)	61.1%	45.5%	64.7%
Terminal Rates (c)	19/34 (56%)	14/33 (42%)	21/35 (60%)
Week of First Observation	48	87	56
Life Table Tests (d)	P=0.439	P=0.094N	P=0.485
Incidental Tumor Tests (d)	P=0.486	P=0.090N	P=0.519
Cochran-Armitage Trend Test (d)	P=0.381		
Fisher Exact Test (d)		P=0.076N	P=0.421
All Sites: Malignant Tumors			
Overall Rates (a)	22/50 (44%)	17/50 (34%)	21/50 (42%)
Adjusted Rates (b)	50.9%	40.2%	50.9%
Terminal Rates (c)	13/34 (38%)	8/33 (24%)	15/35 (43%)
Week of First Observation	48	66	57
Life Table Tests (d)	P=0.413N	P=0.257N	P=0.453N
Incidental Tumor Tests (d)	P=0.320N	P=0.126N	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.459N		
Fisher Exact Test (d)		P=0.206N	P=0.500N
All Sites: All Tumors			
Overall Rates (a)	34/50 (68%)	27/50 (54%)	34/50 (68%)
Adjusted Rates (b)	75.5%	64.1%	77.2%
Terminal Rates (c)	23/34 (68%)	18/33 (55%)	25/35 (71%)
Week of First Observation	48	66	56
Life Table Tests (d)	P=0.456N	P=0.180N	P=0.490N
Incidental Tumor Tests (d)	P=0.359N	P=0.051N	P=0.450N
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.109N	P=0.585N

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

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) Only 18 spleens were examined microscopically.
(f) Incomplete sampling of tissues
(g) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.

TABLE C4a. HISTORICAL INCIDENCE OF ADRENAL GLAND CORTICAL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Adenomas in Vehicle Controls
No 2-year studies by Microbiological Associates are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 20/1,687 (1.2%)
SD (c)	1.86%
Range (d)	
High	3/46
Low	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks. No cortical carcinomas have been observed.
(b) Includes three adenomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 61/1,743 (3.5%)	(c) 5/1,743 (0.3%)	(b,c) 66/1,743 (3.8%)
SD (d)	2.89%	0.72%	3.03%
Range (e)			
High	5/50	1/48	5/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Includes three papillary adenomas, one cystadenoma, NOS, and one papillary cystadenoma, NOS
(c) Includes one papillary adenocarcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
Abscess, NOS			1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic	5 (10%)		1 (2%)
Acanthosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Vegetable foreign body	1 (2%)	1 (2%)	
Cyst, NOS			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute focal			1 (2%)
Abscess, NOS	2 (4%)	1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
Fibrosis, diffuse			†1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(50)	(50)
Inflammation, acute	4 (8%)	7 (14%)	3 (6%)
Inflammation, chronic	1 (2%)		
Foreign material, NOS	1 (2%)	12 (24%)	6 (12%)
#Trachea	(49)	(16)	(48)
Inflammation, acute focal	1 (2%)		
#Lung/bronchiole	(50)	(48)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
#Lung	(50)	(48)	(50)
Congestion, NOS	1 (2%)	1 (2%)	4 (8%)
Hemorrhage	3 (6%)	1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate	27 (54%)	22 (46%)	22 (44%)
Inflammation, acute	2 (4%)		1 (2%)
Inflammation, chronic	1 (2%)		
Pneumonia, interstitial chronic	1 (2%)		
Foreign material, NOS	2 (4%)	7 (15%)	4 (8%)
Pigmentation, NOS	1 (2%)	2 (4%)	
Hyperplasia, adenomatous	12 (24%)	10 (21%)	11 (22%)
Histiocytosis	7 (14%)	6 (13%)	7 (14%)
HEMATOPOIETIC SYSTEM			
*Skin	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
#Bone marrow	(48)	(16)	(50)
Hyperplasia, NOS	3 (6%)	1 (6%)	
Hyperplasia, reticulum cell			1 (2%)
#Spleen	(47)	(18)	(47)
Necrosis, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
Hyperplasia, lymphoid	2 (4%)		2 (4%)
Hematopoiesis	6 (13%)	4 (22%)	
#Splenic follicles	(47)	(18)	(47)
Necrosis, NOS	1 (2%)		2 (4%)
#Lymph node	(47)	(22)	(48)
Inflammation, acute			1 (2%)
Pigmentation, NOS	1 (2%)		
Hyperplasia, lymphoid		1 (5%)	1 (2%)

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(47)	(22)	(48)
Dilatation, NOS		1 (5%)	
Inflammation, chronic			1 (2%)
Necrosis, NOS		1 (5%)	
Pigmentation, NOS	1 (2%)		1 (2%)
Hematopoiesis			1 (2%)
#Mesenteric lymph node	(47)	(22)	(48)
Hemorrhage	19 (40%)	6 (27%)	19 (40%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid	2 (4%)		1 (2%)
Hematopoiesis	7 (15%)	2 (9%)	5 (10%)
#Inguinal lymph node	(47)	(22)	(48)
Inflammation, chronic	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
#Liver	(50)	(48)	(50)
Hematopoiesis	2 (4%)	1 (2%)	
#Thymus	(40)	(14)	(44)
Embryonal duct cyst	8 (20%)		13 (30%)
Atrophy, NOS	1 (3%)		1 (2%)
CIRCULATORY SYSTEM			
#Lung	(50)	(48)	(50)
Embolism, NOS		1 (2%)	
#Heart	(50)	(16)	(50)
Mineralization			1 (2%)
Inflammation, chronic focal	1 (2%)	1 (6%)	1 (2%)
Inflammation, chronic diffuse	1 (2%)		
Fibrosis, focal		1 (6%)	
Scar	1 (2%)		1 (2%)
Fibrosis, multifocal			1 (2%)
*Blood vessel	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Necrosis, focal		1 (2%)	
*Artery	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
*Testicular artery	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Inflammation, acute	1 (2%)		
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS		4 (8%)	4 (8%)
Inflammation, acute	1 (2%)		
*Alveolus dentalis	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
#Salivary gland	(46)	(17)	(50)
Abscess, NOS		1 (6%)	
Inflammation, chronic	20 (43%)	4 (24%)	27 (54%)
Inflammation, chronic focal		2 (12%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(48)	(50)
Mineralization	1 (2%)		
Cyst, NOS	1 (2%)		
Congestion, chronic passive			1 (2%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	7 (14%)	3 (6%)	2 (4%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Necrosis, NOS	2 (4%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)	1 (2%)	2 (4%)
Necrosis, diffuse		1 (2%)	1 (2%)
Cytoplasmic vacuolization			1 (2%)
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Angiectasis	2 (4%)		
#Liver/centrilobular	(50)	(48)	(50)
Inflammation, chronic	1 (2%)		
Necrosis, focal	1 (2%)		
Necrosis, diffuse	1 (2%)		
Cytoplasmic vacuolization	1 (2%)	2 (4%)	
#Liver/hepatocytes	(50)	(48)	(50)
Hyperplasia, focal			1 (2%)
*Gallbladder	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
#Pancreas	(47)	(15)	(47)
Dilatation/ducts	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, active chronic	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
Atrophy, focal		1 (7%)	
Regeneration, NOS		1 (7%)	
#Pancreatic acinus	(47)	(15)	(47)
Atrophy, NOS	1 (2%)		
Atrophy, focal	1 (2%)	1 (7%)	
#Esophagus	(48)	(15)	(50)
Inflammation, acute suppurative			1 (2%)
Inflammation, granulomatous focal	1 (2%)		
#Esophagus/muscularis	(48)	(15)	(50)
Regeneration, NOS	1 (2%)		
#Stomach	(44)	(15)	(47)
Inflammation, acute	1 (2%)		
Crystals, NOS			1 (2%)
#Forestomach	(44)	(15)	(47)
Ulcer, acute		1 (7%)	
Erosion	1 (2%)	1 (7%)	2 (4%)
Hyperplasia, epithelial		1 (7%)	
Hyperplasia, focal	1 (2%)		
#Jejunum	(44)	(14)	(45)
Inflammation, active chronic	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(48)	(49)
Ectopia		2 (4%)	
Mineralization	14 (28%)	1 (2%)	11 (22%)
Hydronephrosis			1 (2%)
Cyst, NOS	2 (4%)	4 (8%)	2 (4%)
Pyelonephritis, NOS			1 (2%)
Pyelonephritis, acute	1 (2%)	3 (6%)	
Inflammation, chronic	9 (18%)	8 (17%)	17 (35%)
Scar	1 (2%)		
Nephropathy	1 (2%)		
Nephrosis, NOS	1 (2%)		
Hyperplasia, tubular cell			1 (2%)
Metaplasia, osseous	1 (2%)		2 (4%)
#Renal papilla	(50)	(48)	(49)
Necrosis, NOS		1 (2%)	1 (2%)
#Kidney/tubule	(50)	(48)	(49)
Cyst, NOS		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
Regeneration, NOS	9 (18%)	9 (19%)	13 (27%)
#Kidney/pelvis	(50)	(48)	(49)
Inflammation, acute		1 (2%)	
#Urinary bladder	(48)	(17)	(47)
Inflammation, acute			1 (2%)
*Urethra	(50)	(50)	(50)
Inflammation, acute focal		2 (4%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(16)	(49)
Hyperplasia, NOS	2 (4%)		2 (4%)
#Adrenal/capsule	(48)	(44)	(48)
Hyperplasia, NOS	37 (77%)	30 (68%)	36 (75%)
#Adrenal cortex	(48)	(44)	(48)
Focal cellular change			1 (2%)
Hypertrophy, NOS		1 (2%)	
Hypertrophy, focal	2 (4%)	2 (5%)	4 (8%)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Adrenal medulla	(48)	(44)	(48)
Hyperplasia, NOS	5 (10%)		1 (2%)
Hyperplasia, focal			1 (2%)
#Thyroid	(48)	(16)	(50)
Embryonal duct cyst	4 (8%)	1 (6%)	5 (10%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal			2 (4%)
Hyperplasia, follicular cell	5 (10%)		
#Parathyroid	(32)	(6)	(29)
Hyperplasia, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*Prepuce	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	3 (6%)	1 (2%)	
Cyst, NOS			1 (2%)
Abscess, NOS	2 (4%)	4 (8%)	2 (4%)
Inflammation, active chronic	3 (6%)	1 (2%)	3 (6%)
Inflammation, chronic	3 (6%)		

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(47)	(14)	(47)
Inflammation, chronic	4 (9%)		4 (9%)
*Seminal vesicle	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Testis	(49)	(16)	(50)
Atrophy, NOS	4 (8%)		1 (2%)
#Testis/tubule	(49)	(16)	(50)
Mineralization	1 (2%)		
*Epididymis	(50)	(50)	(50)
Inflammation, focal			1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
*Vas deferens	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		
NERVOUS SYSTEM			
#Brain/meninges	(49)	(48)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	1 (2%)
#Brain	(49)	(48)	(50)
Corpora amylacea	15 (31%)	21 (44%)	22 (44%)
*Spinal cord	(50)	(50)	(50)
Malacia		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, chronic diffuse		1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS			1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)		3 (6%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	2 (4%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Fracture, NOS		1 (2%)	
*Facial muscle	(50)	(50)	(50)
Hemorrhage			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		1 (2%)
*Thoracic viscera	(50)	(50)	(50)
Foreign material, NOS			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute suppurative			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	1 (2%)	3 (6%)	
Necrosis, NOS	1 (2%)		
Necrosis, fat	1 (2%)	3 (6%)	2 (4%)

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

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Amyloidosis	1 (2%)		
Craniobuccal pouch			
Cyst, NOS	2		5
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
† Multiple occurrence of morphology in the same organ; tissue is counted once only.
# Number of animals examined microscopically at this site

APPENDIX D

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

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

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(19)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)		3 (6%)
Alveolar/bronchiolar carcinoma		1 (5%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			2 (4%)
Malignant lymphoma, undifferentiated type			1 (2%)
Malignant lymphoma, lymphocytic type	3 (6%)		3 (6%)
Malignant lymphoma, histiocytic type	4 (8%)		
Malignant lymphoma, mixed type	3 (6%)	8 (16%)	9 (18%)
#Spleen	(48)	(48)	(50)
Malignant lymphoma, mixed type		1 (2%)	1 (2%)
#Liver	(50)	(48)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
#Uterus	(48)	(48)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Heart	(50)	(17)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Liver	(50)	(48)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(50)
Hepatocellular adenoma	1 (2%)	4 (8%)	2 (4%)
Hepatocellular carcinoma		2 (4%)	2 (4%)
Sarcoma, NOS, metastatic			1 (2%)
#Glandular stomach	(47)	(17)	(48)
Sarcoma, NOS			1 (2%)
#Forestomach	(47)	(17)	(48)
Papilloma, NOS			1 (2%)
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
None			

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(26)	(49)
Adenoma, NOS	1 (2%)		1 (2%)
#Anterior pituitary	(48)	(26)	(49)
Carcinoma, NOS		1 (4%)	
Adenoma, NOS	10 (21%)	7 (27%)	10 (20%)
#Adrenal/capsule	(48)	(15)	(50)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(48)	(15)	(50)
Pheochromocytoma			2 (4%)
#Thyroid	(50)	(17)	(49)
Follicular cell adenoma	3 (6%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	2 (4%)		1 (2%)
*Vagina	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
#Uterus	(48)	(48)	(50)
Endometrial stromal polyp		2 (4%)	2 (4%)
Endometrial stromal sarcoma			1 (2%)
#Uterus/endometrium	(48)	(48)	(50)
Carcinoma, NOS		1 (2%)	
#Ovary	(46)	(26)	(48)
Papillary adenoma			1 (2%)
Cystadenoma, NOS		1 (4%)	1 (2%)
Teratoma, NOS		1 (4%)	1 (2%)
NERVOUS SYSTEM			
#Third ventricle, NOS	(50)	(48)	(50)
Carcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	17	16	9
Moribund sacrifice	4	2	
Terminal sacrifice	25	31	36
Dosing accident	4	1	5

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	27	24	36
Total primary tumors	38	35	51
Total animals with benign tumors	18	14	20
Total benign tumors	23	17	25
Total animals with malignant tumors	14	17	22
Total malignant tumors	15	17	25
Total animals with secondary tumors##	1	1	3
Total secondary tumors	1	1	3
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

• Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
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 BENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 1 4	C 0 4	C 0 6	C 2 0	C 0 3	C 2 3	C 1 6	C 1 8	C 0 8	C 2 7	C 3 7	C 3 9	C 4 6	C 4 9	C 5 0	C 1 1	C 2 4	C 4 0	C 3 8	C 3 2	C 3 6	C 1 0	C 1 7	C 2 6	C 0 1
WEEKS ON STUDY	0 0 3	0 0 4	0 0 5	0 1 9	0 2 2	0 4 0	0 6 5	0 6 6	0 7 1	0 7 1	0 7 1	0 7 1	0 7 5	0 7 7	0 7 7	0 8 3	0 8 3	0 8 5	0 9 0	0 9 1	0 9 5	0 9 6	1 0 3	1 0 3	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																		X							
Alveolar/bronchiolar adenoma									X														X		
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	–	–	–	–	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+
Pancreas	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Squamous cell carcinoma																		X							
Small intestine	+	+	–	+	–	+	+	–	–	+	–	+	+	+	+	+	+	+	+	–	+	–	–	+	+
Large intestine	+	+	–	+	–	–	+	–	–	+	–	+	+	+	+	+	+	–	+	–	+	–	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X										X							X		
Adrenal	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma															X									X	
Parathyroid	–	+	+	+	–	+	+	+	–	+	+	+	–	–	+	+	+	–	–	+	+	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	N	+	+	+	+	N	+	+	+	+	+	+	N	N	+	+	+	+	+	+
Adenocarcinoma, NOS																							X		
Uterus	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Ovary	+	+	+	+	–	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type														X						X		X			
Malignant lymphoma, histiocytic type																				X			X		
Malignant lymphoma, mixed type																X									

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	C 0 2	C 0 5	C 0 7	C 0 9	C 1 2	C 1 3	C 1 5	C 1 9	C 2 1	C 2 2	C 2 5	C 2 8	C 2 9	C 3 0	C 3 1	C 3 3	C 3 4	C 3 5	C 4 1	C 4 2	C 4 3	C 4 4	C 4 5	C 4 7	C 4 8	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma					X															X						4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X							X		X	X						X			X			X		X	11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																									X	3
Parathyroid	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS								X																		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, histiocytic type			X																							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS				X				X						X												3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type															X											3
Malignant lymphoma, histiocytic type									X												X					4
Malignant lymphoma, mixed type																										3

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: LOW DOSE

ANIMAL NUMBER	C 0 6	C 4 0	C 3 7	C 3 9	C 3 8	C 0 5	C 1 3	C 4 7	C 4 3	C 5 0	C 3 2	C 1 1	C 1 6	C 1 4	C 1 8	C 1 7	C 0 4	C 2 7	C 0 1	C 0 2	C 0 3	C 0 7	C 0 8	C 0 9	C 1 0
WEEKS ON STUDY	0 0 3	0 0 4	0 4 5	0 6 1	0 6 3	0 7 0	0 7 1	0 7 4	0 7 6	0 7 7	0 8 1	0 8 2	0 8 5	0 9 0	0 9 1	0 9 2	0 9 6	1 0 0	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Nasal cavity	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	–	–
Thymus	+	+	–	–	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																						X			
Hemangiosarcoma																									X
Malignant lymphoma, histiocytic type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Small intestine	+	+	–	+	+	–	+	+	+	+	–	+	+	+	–	+	+	–	–	–	–	–	–	–	–
Large intestine	+	+	–	+	+	–	+	+	+	+	–	+	+	+	–	+	+	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	–	–	+	–
Carcinoma, NOS																X									
Adenoma, NOS																					X			X	
Adrenal	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	–	–	–	–	–
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Parathyroid	–	–	–	+	+	+	–	–	+	+	+	+	–	–	+	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	+	+	N	+	+	+	N	+	+	+	+	N	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	–	–	–	–	–	–	–
Cystadenoma, NOS																									
Teratoma, NOS																X									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																X									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																					X				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																	X								
Malignant lymphoma, mixed type															X						X				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	C 1 1 2	C 1 1 5	C 1 1 9	C 2 0 0	C 2 2 1	C 2 2 2	C 2 2 3	C 2 2 4	C 2 2 5	C 2 2 6	C 2 2 8	C 2 2 9	C 3 0 0	C 3 1 1	C 3 3 3	C 3 3 4	C 3 3 5	C 3 3 6	C 4 1 1	C 4 1 2	C 4 4 4	C 4 4 5	C 4 4 6	C 4 4 8	C 4 4 9	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	19
Alveolar/bronchiolar carcinoma																									X	1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	48
Malignant lymphoma, mixed type						X																				1
Lymph nodes	–	–	+	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	22
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
DIGESTIVE SYSTEM																										
Salivary gland	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	48
Hepatocellular adenoma									X				X								X			X		4
Hepatocellular carcinoma																X										2
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	48
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	N	*50
Pancreas	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	20
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	19
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	16
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	+	+	+	–	+	–	–	–	+	–	–	+	–	–	–	–	–	+	–	–	–	26
Carcinoma, NOS																										1
Adenoma, NOS						X	X						X			X						X				7
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	17
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	48
Carcinoma, NOS																								X		1
Endometrial stromal polyp								X			X															2
Ovary	–	–	+	+	–	–	–	+	–	–	–	–	–	–	–	+	+	–	+	+	–	+	+	+	+	26
Cystadenoma, NOS																	X									1
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	48
Carcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS											X	X														3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, mixed type		X		X	X			X				X		X												8

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL: HIGH DOSE

ANIMAL NUMBER	C 1 0	C 1 7	C 0 5	C 0 4	C 2 6	C 1 5	C 2 2	C 4 4	C 2 4	C 2 8	C 4 1	C 0 9	C 4 8	C 4 2	C 0 1	C 0 2	C 0 3	C 0 6	C 0 7	C 0 8	C 1 1	C 1 2	C 1 3	C 1 4	C 1 6
WEEKS ON STUDY	0 0 3	0 0 3	0 0 8	0 2 1	0 7 9	0 9 1	0 9 2	0 9 2	0 9 3	0 9 5	0 9 7	1 0 2	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X																		
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	i	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Thymus	−	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic										X															
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma							X																		
Sarcoma, NOS, metastatic								X																	
Hemangiosarcoma					X																				
Malignant lymphoma, histiocytic type												X													
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Sarcoma, NOS								X																	
Small intestine	−	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X	X		X		X						X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma															X			X							
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	−	+	+	+	+	+	−	+	−	+	−	+	−	+	−	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																					X				
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																		X						X	
Endometrial stromal sarcoma																									
Ovary	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Cystadenoma, NOS																					X				
Teratoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS						X			X																
Malignant lymphoma, undifferentiated type																					X				
Malignant lymphoma, lymphocytic type																						X			
Malignant lymphoma, mixed type										X			X	X											

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	C 1 1 8	C 1 1 9	C 2 0 0	C 2 1 1	C 2 2 3	C 2 2 5	C 2 2 7	C 2 2 9	C 3 0 0	C 3 1 1	C 3 2 2	C 3 3 3	C 3 4 4	C 3 5 5	C 3 6 6	C 3 7 7	C 3 8 8	C 3 9 9	C 4 0 0	C 4 3 3	C 4 4 5	C 4 6 6	C 4 7 7	C 4 9 9	C 5 0 0	TOTAL.
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma											X	X														3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type							X																			1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metast																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X								X													2
Hepatocellular carcinoma																					X					2
Sarcoma, NOS, metastatic																										1
Hemangiosarcoma																										1
Malignant lymphoma, histiocytic type																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma, NOS						X																				1
Sarcoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS						X	X							X	X			X		X						11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	−	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	+	+	−	−	+	−	+	−	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										2
Endometrial stromal sarcoma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary adenoma			X																							1
Cystadenoma, NOS																										1
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS											X															1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										2
Malig. lymphoma, undifferentiated type																										1
Malignant lymphoma, lymphocytic type			X																					X		3
Malignant lymphoma, mixed type					X					X	X		X			X	X									9

* Animals necropsied

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

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	(b) 0/19 (0%)	3/50 (6%)
Adjusted Rates (c)	13.1%		8.3%
Terminal Rates (d)	2/26 (8%)		3/36 (8%)
Week of First Observation	71		104
Life Table Test (e)			P=0.349N
Incidental Tumor Test (e)			P=0.499N
Fisher Exact Test (e)			P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	(b) 1/19 (5%)	4/50 (8%)
Adjusted Rates (c)	13.1%		10.6%
Terminal Rates (d)	2/26 (8%)		3/36 (8%)
Week of First Observation	71		95
Life Table Test (e)			P=0.479 N
Incidental Tumor Test (e)			P=0.624N
Fisher Exact Test (e)			P=0.643N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (c)	9.3%	0.0%	8.3%
Terminal Rates (d)	0/26 (0%)	0/32 (0%)	3/36 (8%)
Week of First Observation	77		104
Life Table Tests (e)	P=0.482N	P=0.104N	P=0.519N
Incidental Tumor Tests (e)	P=0.585N	P=0.218N	P=0.661
Cochran-Armitage Trend Test (e)	P=0.601		
Fisher Exact Test (e)		P=0.122N	P=0.661N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (c)	16.8%	3.1%	2.6%
Terminal Rates (d)	2/26 (8%)	1/32 (3%)	0/36 (0%)
Week of First Observation	91	104	102
Life Table Tests (e)	P=0.023N	P=0.072N	P=0.050N
Incidental Tumor Tests (e)	P=0.022N	P=0.117N	P=0.046N
Cochran-Armitage Trend Test (e)	P=0.049N		
Fisher Exact Test (e)		P=0.103N	P=0.103N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	9/50 (18%)	10/50 (20%)
Adjusted Rates (c)	10.3%	27.1%	25.5%
Terminal Rates (d)	2/26 (8%)	8/32 (25%)	7/36 (19%)
Week of First Observation	83	91	95
Life Table Tests (e)	P=0.118	P=0.115	P=0.121
Incidental Tumor Tests (e)	P=0.108	P=0.117	P=0.109
Cochran-Armitage Trend Test (e)	P=0.033		
Fisher Exact Test (e)		P=0.061	P=0.036
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	11/50 (22%)	10/50 (20%)	17/50 (34%)
Adjusted Rates (c)	32.9%	30.1%	40.3%
Terminal Rates (d)	4/26 (15%)	9/32 (28%)	11/36 (31%)
Week of First Observation	77	91	91
Life Table Tests (e)	P=0.373	P=0.331N	P=0.451
Incidental Tumor Tests (e)	P=0.283	P=0.484N	P=0.289
Cochran-Armitage Trend Test (e)	P=0.103		
Fisher Exact Test (e)		P=0.500N	P=0.133

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/50 (2%)	4/48 (8%)	2/50 (4%)
Adjusted Rates (c)	3.0%	13.3%	5.6%
Terminal Rates (d)	0/26 (0%)	4/30 (13%)	2/36 (6%)
Week of First Observation	85	104	104
Life Table Tests (e)	P=0.548	P=0.226	P=0.610
Incidental Tumor Tests (e)	P=0.516	P=0.228	P=0.549
Cochran-Armitage Trend Test (e)	P=0.407		
Fisher Exact Test (e)		P=0.168	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	6/48 (13%)	4/50 (8%)
Adjusted Rates (c)	3.0%	20.0%	10.4%
Terminal Rates (d)	0/26 (0%)	6/30 (20%)	3/36 (8%)
Week of First Observation	85	104	92
Life Table Tests (e)	P=0.310	P=0.084	P=0.296
Incidental Tumor Tests (e)	P=0.259	P=0.085	P=0.208
Cochran-Armitage Trend Test (e)	P=0.170		
Fisher Exact Test (e)		P=0.050	P=0.181
Pituitary Gland: Adenoma			
Overall Rates (a)	10/48 (21%)	(b,f) 7/26 (27%)	10/49 (20%)
Adjusted Rates (c)	35.1%		27.8%
Terminal Rates (d)	8/26 (31%)		10/36 (28%)
Week of First Observation	83		104
Life Table Test (e)			P=0.285N
Incidental Tumor Test (e)			P=0.313N
Fisher Exact Test (e)			P=0.579N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/50 (6%)	(b) 0/17 (0%)	0/49 (0%)
Adjusted Rates (c)	9.8%		0.0%
Terminal Rates (d)	1/26 (4%)		0/36 (0%)
Week of First Observation	77		
Life Table Test (e)			P=0.080N
Incidental Tumor Test (e)			P=0.164N
Fisher Exact Test (e)			P=0.125N
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (c)	11.5%	9.4%	2.8%
Terminal Rates (d)	3/26 (12%)	3/32 (9%)	1/36 (3%)
Week of First Observation	104	104	104
Life Table Tests (e)	P=0.138N	P=0.565N	P=0.196N
Incidental Tumor Tests (e)	P=0.138N	P=0.565N	P=0.196N
Cochran-Armitage Trend Test (e)	P=0.238N		
Fisher Exact Test (e)		P=0.661	P=0.309N
All Sites: Benign Tumors			
Overall Rates (a)	18/50 (36%)	14/50 (28%)	20/50 (40%)
Adjusted Rates (c)	53.1%	43.7%	54.1%
Terminal Rates (d)	11/26 (42%)	14/32 (44%)	19/36 (53%)
Week of First Observation	40	104	103
Life Table Tests (e)	P=0.272N	P=0.099N	P=0.287N
Incidental Tumor Tests (e)	P=0.387N	P=0.158N	P=0.499N
Cochran-Armitage Trend Test (e)	P=0.376		
Fisher Exact Test (e)		P=0.260N	P=0.418

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	14/50 (28%)	17/50 (34%)	22/50 (44%)
Adjusted Rates (c)	40.9%	48.4%	48.7%
Terminal Rates (d)	6/26 (23%)	14/32 (44%)	13/36 (36%)
Week of First Observation	77	91	79
Life Table Tests (e)	P=0.362	P=0.566	P=0.406
Incidental Tumor Tests (e)	P=0.206	P=0.383	P=0.162
Cochran-Armitage Trend Test (e)	P=0.058		
Fisher Exact Test (e)		P=0.333	P=0.072
All Sites: All Tumors			
Overall Rates (a)	27/50 (54%)	24/50 (48%)	36/50 (72%)
Adjusted Rates (c)	72.6%	68.5%	78.1%
Terminal Rates (d)	16/26 (62%)	21/32 (66%)	26/36 (72%)
Week of First Observation	40	91	3
Life Table Tests (e)	P=0.534	P=0.101N	P=0.528N
Incidental Tumor Tests (e)	P=0.268	P=0.196N	P=0.197
Cochran-Armitage Trend Test (e)	P=0.043		
Fisher Exact Test (e)		P=0.345N	P=0.048

(a) Number of tumor-bearing animals/number of animals examined 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 at terminal kill
(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 lower incidence in a dosed group is indicated by (N).
(f) A carcinoma was observed in an eighth animal.

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Abscess, NOS	2 (4%)		
Inflammation, chronic			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(15)	(50)
Vegetable foreign body			1 (2%)
Inflammation, acute	11 (22%)	7 (47%)	14 (28%)
Inflammation, active chronic			1 (2%)
Foreign material, NOS	12 (24%)	9 (60%)	12 (24%)
Metaplasia, squamous		1 (7%)	
#Nasopharynx	(50)	(15)	(50)
Inflammation, acute focal			1 (2%)
Inflammation, acute suppurative	1 (2%)		
Infection, fungal			1 (2%)
#Trachea	(49)	(17)	(50)
Hemorrhage			1 (2%)
Inflammation, acute suppurative		1 (6%)	
#Lung/bronchiole	(50)	(19)	(50)
Inflammation, acute		1 (5%)	1 (2%)
Necrosis, NOS	1 (2%)		
#Lung	(50)	(19)	(50)
Congestion, NOS	1 (2%)	1 (5%)	
Edema, NOS	1 (2%)		1 (2%)
Hemorrhage	1 (2%)	1 (5%)	2 (4%)
Lymphocytic inflammatory infiltrate	32 (64%)	12 (63%)	31 (62%)
Inflammation, interstitial			1 (2%)
Inflammation, acute focal		1 (5%)	1 (2%)
Pneumonia, interstitial chronic			1 (2%)
Foreign material, NOS	3 (6%)	7 (37%)	4 (8%)
Hyperplasia, adenomatous	4 (8%)		5 (10%)
Histiocytosis	7 (14%)	1 (5%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(17)	(50)
Hyperplasia, NOS	8 (17%)	6 (35%)	1 (2%)
#Spleen	(48)	(48)	(50)
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	9 (19%)	2 (4%)	11 (22%)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	5 (10%)	5 (10%)
Hematopoiesis	12 (25%)	10 (21%)	1 (2%)
#Splenic capsule	(48)	(48)	(50)
Inflammation, chronic focal			1 (2%)
#Splenic follicles	(48)	(48)	(50)
Necrosis, NOS	2 (4%)	3 (6%)	
#Mandibular lymph node	(48)	(22)	(46)
Hemorrhage			1 (2%)
Inflammation, acute focal		1 (5%)	
Degeneration, cystic	1 (2%)		
Necrosis, diffuse	1 (2%)		
Pigmentation, NOS			2 (4%)
Hyperplasia, lymphoid	2 (4%)	2 (9%)	
Hematopoiesis			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Bronchial lymph node	(48)	(22)	(46)
Hyperplasia, lymphoid		1 (5%)	
#Mesenteric lymph node	(48)	(22)	(46)
Cyst, NOS	1 (2%)		1 (2%)
Hemorrhage	4 (8%)	1 (5%)	2 (4%)
Hemorrhagic cyst	1 (2%)		
Inflammation, acute	1 (2%)	2 (9%)	
Necrosis, NOS		1 (5%)	
Hematopoiesis	1 (2%)		
#Iliac lymph node	(48)	(22)	(46)
Inflammation, acute	1 (2%)		
#Nasal cavity	(50)	(15)	(50)
Hyperplasia, lymphoid			1 (2%)
#Liver	(50)	(48)	(50)
Leukocytosis, NOS	1 (2%)		
Hematopoiesis	11 (22%)	9 (19%)	1 (2%)
#Duodenum	(42)	(13)	(46)
Hyperplasia, lymphoid	1 (2%)		
#Adrenal/capsule	(48)	(15)	(50)
Hematopoiesis	1 (2%)		
#Adrenal cortex	(48)	(15)	(50)
Hematopoiesis	4 (8%)		
#Thymus	(41)	(13)	(45)
Embryonal duct cyst	9 (22%)		15 (33%)
Inflammation, acute	1 (2%)	1 (8%)	
Atrophy, NOS	1 (2%)	1 (8%)	
Atrophy, diffuse	1 (2%)		
CIRCULATORY SYSTEM			
*Larynx	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Lung	(50)	(19)	(50)
Embolus, septic	1 (2%)		
#Heart	(50)	(17)	(50)
Congestion, NOS		1 (6%)	
Inflammation, suppurative	1 (2%)		
Inflammation, acute		1 (6%)	
Inflammation, chronic	2 (4%)	1 (6%)	1 (2%)
#Myocardium	(50)	(17)	(50)
Necrosis, NOS	1 (2%)		
*Blood vessel	(50)	(50)	(50)
Inflammation, necrotizing		1 (2%)	
*Aorta	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
*Vaginal artery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Pancreas	(48)	(20)	(48)
Periarteritis	1 (2%)		
*Mesentery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Urinary bladder	(49)	(16)	(50)
Periarteritis	1 (2%)		
#Uterus	(48)	(48)	(50)
Thrombosis, NOS		1 (2%)	1 (2%)
#Anterior pituitary	(48)	(26)	(49)
Thrombosis, NOS			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(17)	(49)
Inflammation, acute	1 (2%)		
Inflammation, chronic	19 (40%)	5 (29%)	26 (53%)
#Liver	(50)	(48)	(50)
Cyst, NOS			1 (2%)
Congestion, acute passive	1 (2%)		
Inflammation, acute	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic	13 (26%)	8 (17%)	16 (32%)
Necrosis, NOS	4 (8%)	3 (6%)	1 (2%)
Pigmentation, NOS		1 (2%)	1 (2%)
Mitotic alteration	1 (2%)		2 (4%)
Cytoplasmic vacuolization	2 (4%)		1 (2%)
Focal cellular change	1 (2%)		1 (2%)
Angiectasis	1 (2%)		
#Liver/centrilobular	(50)	(48)	(50)
Necrosis, NOS	1 (2%)		
Necrosis, diffuse			2 (4%)
Cytoplasmic vacuolization	1 (2%)		
*Gallbladder	(50)	(50)	(50)
Inflammation, acute suppurative	1 (2%)		
Inflammation, chronic	1 (2%)		3 (6%)
*Gallbladder/serosa	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Bile duct	(50)	(48)	(50)
Cyst, NOS		1 (2%)	
#Pancreas	(48)	(20)	(48)
Dilatation/ducts	1 (2%)	2 (10%)	1 (2%)
Inflammation, acute	1 (2%)	5 (25%)	
Inflammation, active chronic			1 (2%)
Inflammation, chronic	3 (6%)	2 (10%)	5 (10%)
Necrosis, fat			1 (2%)
#Pancreatic acinus	(48)	(20)	(48)
Atrophy, NOS	1 (2%)		
Atrophy, focal			1 (2%)
Atrophy, diffuse	1 (2%)	2 (10%)	1 (2%)
#Esophagus	(50)	(17)	(50)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic			1 (2%)
#Glandular stomach	(47)	(17)	(48)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		
#Forestomach	(47)	(17)	(48)
Erosion			2 (4%)
Hyperplasia, focal	1 (2%)		1 (2%)
#Ileum	(42)	(13)	(46)
Inflammation, acute suppurative		1 (8%)	
URINARY SYSTEM			
#Kidney	(50)	(19)	(50)
Mineralization	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Pyelonephritis, acute		2 (11%)	
Abscess, NOS	1 (2%)		
Pyelonephritis, acute/chronic	1 (2%)	1 (5%)	
Inflammation, chronic	21 (42%)	5 (26%)	15 (30%)
Scar	2 (4%)		1 (2%)
Nephrosis, NOS	1 (2%)		1 (2%)
#Renal papilla	(50)	(19)	(50)
Necrosis, NOS			1 (2%)
#Kidney/tubule	(50)	(19)	(50)
Regeneration, NOS	1 (2%)		2 (4%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Urinary bladder	(49)	(16)	(50)
Inflammation, chronic	7 (14%)		2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(26)	(49)
Cyst, NOS			1 (2%)
Hyperplasia, NOS	11 (23%)	3 (12%)	9 (18%)
Hyperplasia, focal			1 (2%)
Angiectasis	2 (4%)		5 (10%)
#Adrenal/capsule	(48)	(15)	(50)
Cyst, NOS			1 (2%)
Inflammation, acute focal	1 (2%)		
Hyperplasia, NOS	37 (77%)	14 (93%)	44 (88%)
Hyperplasia, focal	1 (2%)		1 (2%)
#Adrenal cortex	(48)	(15)	(50)
Congestion, NOS	1 (2%)	1 (7%)	
Amyloidosis	1 (2%)		
Metamorphosis, fatty			1 (2%)
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, NOS	2 (4%)		1 (2%)
Hyperplasia, focal		1 (7%)	
#Adrenal medulla	(48)	(15)	(50)
Hyperplasia, NOS			3 (6%)
#Thyroid	(50)	(17)	(49)
Embryonal duct cyst	3 (6%)	2 (12%)	1 (2%)
Inflammation, chronic	5 (10%)		7 (14%)
Hyperplasia, follicular cell	3 (6%)		6 (12%)
#Parathyroid	(38)	(8)	(34)
Hyperplasia, NOS	1 (3%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	2 (4%)	1 (2%)	6 (12%)
Inflammation, chronic	1 (2%)		
*Clitoral gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
*Vagina	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		
#Uterus	(48)	(48)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	2 (4%)	2 (4%)	1 (2%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute suppurative	6 (13%)	6 (13%)	1 (2%)
Abscess, NOS	3 (6%)	6 (13%)	1 (2%)
Necrosis, diffuse	1 (2%)		
Angiectasis	1 (2%)		
#Cervix/uteri	(48)	(48)	(50)
Mineralization			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic	1 (2%)		2 (4%)
#Uterus/endometrium	(48)	(48)	(50)
Hyperplasia, cystic	24 (50%)	31 (65%)	38 (76%)
#Fallopian tube	(48)	(48)	(50)
Inflammation, chronic	3 (6%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Ovary	(46)	(26)	(48)
Mineralization	2 (4%)		1 (2%)
Cyst, NOS	14 (30%)	12 (46%)	20 (42%)
Hemorrhagic cyst	2 (4%)		1 (2%)
Inflammation, acute		2 (8%)	
Inflammation, acute suppurative		1 (4%)	
Abscess, NOS	2 (4%)	1 (4%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(48)	(50)
Lymphocytic inflammatory infiltrate		2 (4%)	3 (6%)
Fibrosis, multifocal			1 (2%)
#Brain	(50)	(48)	(50)
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate			3 (6%)
Corpora amylacea	14 (28%)	15 (31%)	25 (50%)
#Cerebellum	(50)	(48)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Atrophy, focal	1 (2%)		
*Spinal cord	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, focal			1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	1 (2%)		
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous dysplasia	8 (16%)		8 (16%)
*Skeletal muscle	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Hematocele	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, acute	1 (2%)	9 (18%)	
Inflammation, acute suppurative	3 (6%)		
Inflammation, active chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Pigmentation, NOS		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BENZYL ALCOHOL (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Pleura	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute	1 (2%)	5 (10%)	
Inflammation, acute focal	1 (2%)		
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute suppurative	1 (2%)		
*Epicardium	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, acute suppurative	1 (2%)		
Inflammation, chronic focal		1 (2%)	
*Mesentery	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, acute suppurative	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Necrosis, fat	2 (4%)	2 (4%)	6 (12%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF

BENZYL ALCOHOL

TABLE E1. MUTAGENICITY OF BENZYL ALCOHOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	132 ± 6.7	142 ± 5.1	83 ± 3.3	122 ± 8.5	88 ± 8.4	134 ± 4.7
	100	134 ± 3.2	137 ± 9.2	69 ± 2.0	125 ± 6.7	117 ± 11.9	137 ± 3.2
	333	115 ± 3.7	133 ± 6.4	88 ± 4.8	131 ± 7.2	115 ± 6.4	138 ± 8.2
	1,000	110 ± 8.9	137 ± 10.7	70 ± 6.7	148 ± 9.5	111 ± 7.8	122 ± 10.5
	3,333	(c) 105 ± 7.2	135 ± 6.5	66 ± 4.0	(c) 134 ± 8.4	119 ± 11.3	(c) 138 ± 4.6
	5,000	--	(c) 135 ± (8.5	--	--	--	--
	6,666	Toxic	--	(c) 66 ± 3.4	(c) 120 ± 11.6	(c) 98 ± 3.2	(c) 124 ± 12.3
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,819 ±110.1	2,012 ± 17.2	1,289 ± 70.8	2,056 ± 17.1	939 ± 72.6	1,611 ± 59.0
TA1535	0	30 ± 6.6	18 ± 2.1	8 ± 1.2	8 ± 2.0	12 ± 2.7	11 ± 1.2
	100	23 ± 4.9	22 ± 2.1	7 ± 1.8	8 ± 2.1	9 ± 2.7	10 ± 3.3
	333	29 ± 2.3	22 ± 3.2	10 ± 1.7	13 ± 1.5	7 ± 1.8	10 ± 3.2
	1,000	25 ± 1.2	17 ± 2.3	9 ± 0.9	11 ± 0.7	8 ± 2.5	13 ± 2.7
	3,333	26 ± 3.3	25 ± 0.3	13 ± 2.8	13 ± 2.7	13 ± 0.7	12 ± 1.9
	5,000	--	26 ± 3.3	--	--	--	--
	6,666	Toxic	--	9 ± 1.2	(c) 12 ± 0.9	(c) 8 ± 1.0	(c) 10 ± 2.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,266 ± 53.7	1,384 ± 33.3	69 ± 6.6	123 ± 3.4	43 ± 1.7	70 ± 2.1
TA1537	0	8 ± 0.9	4 ± 0.9	9 ± 0.7	9 ± 0.9	8 ± 2.5	7 ± 0.6
	100	5 ± 0.9	9 ± 2.6	8 ± 0.9	5 ± 1.5	7 ± 2.1	9 ± 0.9
	333	6 ± 1.5	7 ± 2.6	6 ± 0.3	5 ± 2.2	8 ± 1.5	8 ± 0.7
	1,000	7 ± 1.2	5 ± 0.6	6 ± 0.6	7 ± 1.2	7 ± 1.5	7 ± 0.9
	3,333	8 ± 1.5	4 ± 1.7	8 ± 1.2	7 ± 2.1	8 ± 3.6	9 ± 1.5
	5,000	--	8 ± 1.2	--	--	--	--
	6,666	Toxic	--	7 ± 0.9	(c) 8 ± 0.7	(c) 8 ± 3.1	(c) 6 ± 2.0
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	157 ± 15.3	777 ± 30.3	69 ± 10.1	136 ± 4.9	60 ± 0.7	86 ± 5.9
TA98	0	16 ± 3.5	14 ± 3.5	31 ± 5.4	30 ± 2.5	30 ± 0.6	29 ± 1.7
	100	20 ± 4.4	13 ± 0.7	30 ± 0.7	27 ± 2.1	27 ± 1.5	24 ± 1.7
	333	20 ± 1.0	13 ± 4.0	31 ± 5.1	28 ± 5.2	32 ± 2.7	26 ± 4.2
	1,000	15 ± 0.9	18 ± 2.4	33 ± 4.0	22 ± 4.1	24 ± 3.6	28 ± 5.9
	3,333	14 ± 0.9	14 ± 1.0	31 ± 3.6	25 ± 3.2	34 ± 5.0	28 ± 2.9
	5,000	--	15 ± 3.0	--	--	--	--
	6,666	(c) 20 ± 3.8	--	32 ± 3.3	(c) 27 ± 1.2	30 ± 3.8	(c) 19 ± 1.5
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	1,205 ± 23.7	1,580 ± 32.0	1,093 ± 30.3	1,525 ± 84.5	804 ± 29.7	922 ± 20.4

(a) Study performed at EG&G Mason Research Institute. 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 liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY BENZYL ALCOHOL 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 (d)		62.0 ± 5.3	100.0 ± 13.1	90.7 ± 9.3	50.3 ± 9.8
Benzyl alcohol	156.25	88.5 ± 3.5	110.5 ± 15.5	91.5 ± 2.5	34.5 ± 0.5
	312.5	70.0 ± 1.0	105.0 ± 7.0	121.0 ± 2.0	57.5 ± 1.5
	625	96.0 ± 8.0	109.0 ± 23.0	165.0 ± 1.0	58.0 ± 5.0
	1,250	84.0 ± 11.0	106.5 ± 27.5	140.0 ± 6.0	57.0 ± 10.0
	2,500	88.0 ± 6.0	80.0 ± 2.0	175.5 ± 5.5	67.0 ± 2.0
	(e) 5,000	85	14	384	(f) 150
Methyl methanesulfonate	15	27.0 ± 1.0	25.5 ± 1.5	181.5 ± 31.5	(f) 222.5 ± 31.5
Trial 2					
Dimethyl sulfoxide (g)		77.5 ± 5.1	100.0 ± 1.0	87.8 ± 11.1	38.0 ± 3.8
Benzyl alcohol	2,500	84.5 ± 2.5	96.0 ± 1.0	94.5 ± 2.5	37.5 ± 0.5
	3,000	74.0 ± 7.0	63.0 ± 7.0	94.5 ± 3.5	43.0 ± 6.0
	3,500	83.5 ± 8.5	64.5 ± 8.5	107.5 ± 3.5	43.0 ± 3.0
	4,000	49.5 ± 13.5	30.5 ± 10.5	90.0 ± 38.0	58.0 ± 10.0
	4,500	90.0 ± 14.0	20.5 ± 0.5	282.5 ± 19.5	(f) 106.0 ± 9.0
	5,000	Lethal	--	--	--
Methyl methanesulfonate	15	29.0 ± 2.0	30.0 ± 1.0	173.5 ± 20.5	(f) 203.0 ± 39.0
Trial 3					
Dimethyl sulfoxide (g)		83.5 ± 10.0	100.0 ± 3.8	116.5 ± 8.1	47.8 ± 4.2
Benzyl alcohol	250	74.0 ± 14.0	79.5 ± 6.5	86.5 ± 3.5	40.0 ± 6.0
	500	83.5 ± 4.5	87.5 ± 1.5	100.5 ± 9.5	40.5 ± 1.5
	1,500	63.5 ± 3.5	61.5 ± 6.5	63.0 ± 12.0	32.5 ± 4.5
	2,500	83.5 ± 1.5	46.0 ± 7.0	88.0 ± 12.0	35.0 ± 4.0
	3,500	Lethal	--	--	--
Methyl methanesulfonate	15	36.5 ± 3.5	22.5 ± 1.5	244.0 ± 38.0	(f) 227.0 ± 55.0
+S9 (h)					
Dimethyl sulfoxide (g)		64.8 ± 1.5	100.0 ± 4.4	56.0 ± 4.7	29.3 ± 2.8
Benzyl alcohol	250	68.0 ± 2.0	106.5 ± 0.5	75.0 ± 3.0	36.5 ± 0.5
	500	55.5 ± 4.5	84.0 ± 5.0	53.5 ± 7.5	33.0 ± 7.0
	1,500	65.0 ± 5.0	83.0 ± 0.0	70.0 ± 1.0	36.5 ± 2.5
	2,500	66.0 ± 9.0	69.0 ± 7.0	47.0 ± 13.0	23.5 ± 3.5
	3,500	Lethal	--	--	--
Methylcholanthrene	2.5	60.0 ± 3.0	57.5 ± 1.5	294.5 ± 32.5	(f) 163.5 ± 9.5

TABLE E2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY BENZYL ALCOHOL IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate; unless otherwise indicated, the average for two 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 of replicate trials for 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) Results presented are the average of three tests.
(e) Results are for one test only; the dose in the other test was lethal.
(f) 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.
(g) Results presented are the average of four tests.
(h) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent (dimethyl sulfoxide).

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BENZYL ALCOHOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,027	446	0.43	8.9	26.0	--
Benzyl alcohol	16	50	1,041	448	0.43	9.0	26.0	101.1
	50	50	1,044	489	0.47	9.8	26.0	110.1
	160	50	1,037	466	0.45	9.3	26.0	104.5
	500	50	1,048	481	0.46	9.6	26.0	107.9
	1,600	0	--	--	--	--	--	--
Mitomycin C	0.001	50	1,040	699	0.67	14.0	26.0	157.3
	0.01	50	1,047	2,367	2.26	47.3	26.0	531.5
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,038	442	0.43	8.8	27.0	--
Benzyl alcohol	500	50	1,042	490	0.47	9.8	27.0	111.4
	750	50	1,033	507	0.49	10.1	27.0	114.8
	1,000	50	1,039	505	0.49	10.1	27.0	114.8
	1,250	50	1,034	569	0.55	11.4	27.0	129.5
	1,500	0	--	--	--	--	--	--
Mitomycin C	0.001	50	1,053	1,343	1.28	26.9	27.0	305.7
	0.01	10	210	769	3.66	76.9	27.0	873.9
+S9 (d)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,042	395	0.38	7.9	26.5	--
Benzyl alcohol	16	50	1,044	384	0.37	7.7	26.5	97.5
	50	50	1,046	456	0.44	9.1	26.5	115.2
	160	50	1,046	436	0.42	8.7	26.5	110.1
	500	50	1,046	446	0.43	8.9	26.5	112.7
	1,600	50	1,048	456	0.44	9.1	26.5	115.2
	5,000	0	--	--	--	--	--	--
Cyclophosphamide	0.3	50	1,043	490	0.47	9.8	26.5	124.1
	2	50	1,043	1,168	1.12	23.4	26.5	296.2
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,045	431	0.41	8.6	26.0	--
Benzyl alcohol	500	50	1,046	445	0.43	8.9	26.0	103.5
	1,600	50	1,043	477	0.46	9.5	26.0	110.5
	3,000	50	1,040	474	0.46	9.5	26.0	110.5
	4,000	31	647	330	0.51	10.6	26.0	123.3
	5,000	0	--	--	--	--	--	--
Cyclophosphamide	0.3	50	1,041	636	0.61	12.7	26.0	147.7
	2	10	210	312	1.49	31.2	26.0	362.8

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BENZYL ALCOHOL (Continued)

(a) Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (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 in treated culture expressed as a percent of the SCEs/cell in the control culture
(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. Then cells were 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 E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BENZYL ALCOHOL (a)

Dose (µg/ml)	Total Cells	−S9 (b) No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	+S9 (c) No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1--Harvest time 12.5 h					**Trial 1**--Harvest time 12.0 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	4	0.04	3		100	1	0.01	1
Benzyl alcohol					Benzyl alcohol				
160	100	2	0.02	2	50	100	1	0.01	1
500	100	3	0.03	3	160	100	2	0.02	2
1,600	100	2	0.02	2	500	100	4	0.04	4
5,000	100	3	0.03	2	1,600	100	2	0.02	2
					5,000	100	2	0.02	2
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.25	100	38	0.38	28	15	100	31	0.31	25
1	50	31	0.62	44	50	100	49	0.49	38
Trial 2--Harvest time 12.0 h					**Trial 2**--Harvest time 15.0 h (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3		100	1	0.01	1
Benzyl alcohol					Benzyl alcohol				
2,000	100	4	0.04	4	500	100	1	0.01	1
3,000	100	5	0.05	4	1,600	100	2	0.02	2
4,000	100	18	0.18	12	3,000	100	2	0.02	2
5,000	20	6	0.30	20	4,000	100	26	0.26	22
Summary: Positive					Summary: Weakly positive				
Mitomycin C					Cyclophosphamide				
0.25	100	39	0.39	27	15	100	72	0.72	39
1	50	45	0.90	56					
Trial 3--Harvest time 12.0 h					**Trial 3**--Harvest time 12.3 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0		100	0	0.00	0
Benzyl alcohol					Benzyl alcohol				
250	100	1	0.01	1	1,600	100	0	0.00	0
500	100	0	0.00	0	3,000	100	2	0.02	2
1,600	100	1	0.01	1	4,000	100	69	0.69	52
3,000	0	--	--	--	5,000	0	--	--	--
Summary: Negative					Summary: Weakly positive				
Mitomycin C					Cyclophosphamide				
1	100	67	0.67	46	15	100	24	0.24	22
					50	50	59	1.18	72

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BENZYL ALCOHOL (Continued)

−S9					+S9				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 4--Harvest time 17.0 h (d)					Trial 4--Harvest time 18.0 h (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0		100	3	0.03	3
Benzyl alcohol					Benzyl alcohol				
500	100	2	0.02	2	1,600	100	5	0.05	4
1,600	100	1	0.01	1	3,000	100	3	0.03	3
3,000	100	1	0.01	1	4,000	100	49	0.49	32
4,000	0	--	--	--	5,000	0	--	--	--
Summary: Negative					Summary: Weakly positive				
Mitomycin C					Cyclophosphamide				
1	100	67	0.67	46	15	100	29	0.29	21
					50	50	40	0.80	46

(a) Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (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, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) 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 (dimethyl sulfoxide) 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.
(d) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect 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 male mice. 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 (6,12,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (6 mo) Sendai (18 mo)	MHV (mouse hepatitis virus) (12,18,24 mo) *M. pul.* (*Mycoplasma pulmonis*) (12,18,24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,12 mo)	RCV (rat coronavirus) Sendai (18 mo)	*M. pul.*

II. Results

Results are presented in Table F1.

TABLE F1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ALCOHOL (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	9/10	Sendai
	8/9	RCV
12	9/10	PVM
	10/10	Sendai
18	7/8	PVM
	8/8	Sendai
	1/1	RCV
(b) 24	--	--
MICE		
6	7/10	Sendai
12	8/10	Sendai
18	10/10	Sendai
24	1/5	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control male mice just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) Due to an oversight, the laboratory did not collect samples from rats at 24 months.

APPENDIX G

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

Pelleted Diet: December 1980 to January 1983

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

TABLE G1. 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 G2. VITAMINS AND MINERALS IN NIH 07 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 G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.8 ± 2.0	14.0-21.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.25 ± 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 ± 0.06	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two lots of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One lot (7/22/81) not analyzed for thiamine

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.17	<0.29-1.06	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.00 ± 0.74	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
Nitrite nitrogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
BHA (ppm) (d)	6.68 ± 4.95	<0.4-17.0	24
BHT (ppm) (d)	3.45 ± 2.56	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	40,557 ± 29,431	4,900-88,000	23
Aerobic plate count (CFU/g) (f)	77,617 ± 183,824	4,900-930,000	24
Coliform (MPN/g) (g)	16.6 ± 2.9	<3-93	22
Coliform (MPN/g) (h)	80.20 ± 236.3	<3-1,100	24
E. coli (MPN/g) (i)	<3		24
Total nitrosamines (ppb) (j,k)	4.63 ± 4.19	<0.8-18.5	21
Total nitrosamines (ppb) (j,l)	27.15 ± 64.35	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (j,k)	3.43 ± 3.96	0.8-16.5	21
N-Nitrosodimethylamine (ppb) (j,l)	25.71 ± 64.90	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
Pesticides (ppm)			
α-BHC (a,m)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (n)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (n)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) Mean, standard deviation, and range exclude one high value of 930,000 obtained for the lot produced on 12/22/82 (CFU = colony forming unit).
(f) Mean, standard deviation, and range include the high value listed in footnote (e).
(g) Mean, standard deviation, and range exclude one high value of 1,100 obtained for the lot produced on 12/16/80 and one high value of 460 obtained in the lot produced on 9/23/82 (MPN = most probable number).
(h) Mean, standard deviation, and range include the high values listed in footnote (g).
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb for lots produced on 1/26/81, 2/23/81, and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC = hexachlorocyclohexane or benzene hexachloride.
(n) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(o) Thirteen lots contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The experimental data, documents, and pathology specimens for the 2-year toxicology and carcinogenesis studies of benzyl alcohol in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (implemented by the NTP beginning October 1, 1981). The animal studies were conducted for the NTP by Microbiological Associates, Bethesda, Maryland. Administration of benzyl alcohol in corn oil by gavage began on March 30, 1981, for rats and January 5, 1981, for mice. The retrospective audit of archival study records was conducted for the NIEHS at the NTP Archives during April 1987 by Program Resources, Inc. The full audit report is on file at the NIEHS and includes a review of:

1. All inlife records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
2. All clinical observations recorded for the 2-year studies and a 10% random sample of animals' body weights.
3. All inlife records pertaining to protocols, correspondence, environmental conditions, animal husbandry, animal identification, masses, disposition codes, mortality, and correlation of final inlife observations of masses with necropsy findings.
4. All information pertaining to cage rotation.
5. All chemistry records.
6. Pathology tables and all postmortem records concerning identification, disposition codes, condition codes, correlation between gross observations and microscopic diagnoses, and tissue accountability.
7. All slides from the rat studies for the presence of eye sections.
8. Labels on all wet tissue bags for verification with animal identification.
9. Wet tissues from a 10% random sample of the study animals as well as wet tissues from animals that had inlife or gross observations without a corresponding microscopic diagnosis in order to verify animal identification and to examine for untrimmed potential lesions.
10. Blocks and slides of tissues from the random 10% sample of the study animals to examine for proper match and inventory.
11. The comparison between diagnoses listed in the red-lined pathology tables from a 10% random sample of study animals with the diagnoses presented in the final pathology tables for verification of data entry.
12. Original and derived data in the Preliminary Draft of the NTP Technical Report (audited by Program Resources, Inc., during June 1987).

The audit showed that study procedures and events were documented adequately by the study records, with a few exceptions. Study records indicated that cages were rotated for the last 10 weeks of the studies. Disposition of surplus animals and the quantity of study chemical received initially were not documented. Recalculated dose analysis results were incorporated into the Technical Report.

Audit of the pathology specimens showed that residual tissues were present for all but one rat and were labeled properly. For 64 rats examined, all were identified correctly. Ear tags were present and correct for 49/55 mice examined. Although the tag for one mouse lacked a dose group code and tags for five other mice were missing, identity was confirmed in each of these instances because sex organs and necropsy descriptions were consistent with residual tissues. The audit identified few untrimmed potential lesions (12 rats and 5 mice) and some noncorrelations between gross observations and microscopic diagnoses (12 in rats and 8 in mice), but these were not in target organs and did not affect the results of studies. These minor audit findings are considered to be of no significance. Full details are presented in the audit report.

In conclusion, the study records at the NTP Archives support the data and results presented in this NTP Technical Report.

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