NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 369

TOXICOLOGY AND CARCINOGENESIS STUDIES OF α-METHYLBENZYL ALCOHOL

(CAS NO. 98-85-1)

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

FOREWORD

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

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

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a comprehensive audit before being presented for public review. This Technical Report has been reviewed and approved by the NTP Board of Scientific Counselors' Peer Review Panel in public session; the interpretations described herein represent the official scientific position of the NTP.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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(CAS NO. 98-85-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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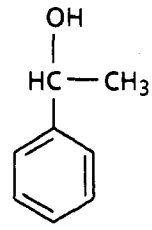

α-METHYLBENZYL ALCOHOL

CAS No. 98-85-1

$C_8H_{10}O$ Molecular weight 122.2

Synonyms: Styrallyl alcohol; styralyl alcohol; α-methylbenzenemethanol; phenylmethylcarbinol; 1-phenethyl alcohol

ABSTRACT

Toxicology and carcinogenesis studies of α-methylbenzyl alcohol (greater than 99% pure), a cosmetic ingredient and food flavoring agent, were conducted by administering the chemical in corn oil by gavage to groups of F344/N rats and $B6C3F_1$ mice of each sex for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, and Chinese hamster ovary (CHO) cells. α-Methylbenzyl alcohol was nominated for study by the National Cancer Institute because of the potential for widespread human exposure.

Sixteen-Day and Thirteen-Week Studies: The doses used in 16-day studies for rats and mice ranged between 125 and 2,000 mg/kg. Six of 10 rats and all mice dosed at 2,000 mg/kg died. In addition, because 7/9 mice dosed at 1,000 mg/kg died, the doses selected for the 13-week studies for mice (47-750 mg/kg) were half those used for rats (93-1,500 mg/kg).

In the 13-week studies, deaths of 1/10 male and 3/10 female rats dosed at 1,500 mg/kg were compound related; none of the mice died. Body weight gain was reduced in rats at 1,500 mg/kg; there were no significant histopathologic lesions in either rats or mice. The only compound-related effects were ataxia, labored breathing, and lethargy for up to 30 minutes after dosing in rats and mice given the two highest doses and increases in liver weight to body weight ratios for male rats given the three highest doses and for female rats at all doses.

Based on the pattern of mortality and the effects on body weight gain in the short-term studies, doses of 375 and 750 mg/kg α-methylbenzyl alcohol were administered in corn oil by gavage, 5 days per week for 103 weeks, to groups of 50 rats and 50 mice of each sex.

Two-Year Studies: Significant reduction in body weight gain commenced at weeks 20-30 in high dose male and female rats, and body weights were 20%-30% below those of vehicle controls at study termination. In the low dose groups, body weight reduction occurred only in male rats during the last 10 weeks of the study. After 80 weeks, 60% of the high dose rats and 80%-100% of the low dose and vehicle control rats were alive; thereafter, the number of deaths in the chemically exposed groups increased sharply so that, at the end of 2 years, final survival for vehicle control, low dose, and high dose rats was 35/50, 8/50, and 1/50 for males and 34/50, 25/50, and 11/50 for females. There were a large number of gavage accidents in these studies (1, 9, and 8 for male rats and 1, 4, and 14 for female rats), but these accidents did not contribute to the increase in mortality after week 80, as all but 4 of these occurred earlier.

Mortality in the last quarter of the study was thought to be due to the effects of cumulative toxicity of α-methylbenzyl alcohol on a renal excretory system already compromised by aging. Renal nephropathy that commonly occurs during aging was found in all groups of rats, but the severity was greater in the male rats dosed with α-methylbenzyl alcohol. In addition, a collection of nonneoplastic lesions (parathyroid hyperplasia, calcification of the heart and glandular stomach, and fibrous osteodystrophy of bone) was found in the dosed male rats; these lesions were probably secondary to mineral imbalance arising from renal dysfunction.

Since survival was poor in low and high dose male and high dose female rats, the sensitivity of the study for detecting a carcinogenic effect in these groups was reduced. Despite this limitation, there were dose-related increases in the incidences of renal tubular cell adenomas or adenocarcinomas (combined) in male rats (vehicle control, 0/50; low dose, 2/50; high dose, 5/50). In addition, transitional cell papillomas of the urinary bladder were observed in one high dose male and two high dose female rats.

In mice, a reduction in body weight gain was apparent in the high dose groups of males and females. Final survival rates in mice were similar among groups (male: 39/49; 40/50; 28/50; female: 41/50; 41/50; 38/50). No neoplastic or nonneoplastic lesions were attributed to α-methylbenzyl alcohol administration in mice of either sex.

Genetic Toxicology: α-Methylbenzyl alcohol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in the presence or absence of exogenous metabolic activation. α-Methylbenzyl alcohol produced a positive response without activation in the mouse L5178Y/TK$^{+/-}$ lymphoma assay for induction of trifluorothymidine resistance; it was not tested with activation. In cytogenetic tests with CHO cells, α-methylbenzyl alcohol induced chromosomal aberrations in the presence, but not the absence, of metabolic activation; no induction of sister chromatid exchanges was observed in CHO cells after exposure to α-methylbenzyl alcohol.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of α-methylbenzyl alcohol for male F344/N rats, as shown by increased incidences of renal tubular cell adenomas and adenomas or adenocarcinomas (combined). There was *no evidence of carcinogenic activity* for female F344/N rats administered 375 or 750 mg/kg. Renal toxicity characterized by severe nephropathy and related secondary lesions was observed in the dosed rats, and excessive mortality occurred during the last quarter of the studies. Poor survival reduced the sensitivity of the studies for detecting the presence of a carcinogenic response both in chemically exposed groups of male rats and in the high dose group of female rats. There was *no evidence of carcinogenic activity* of α-methylbenzyl alcohol for male or female B6C3F$_1$ mice administered 375 or 750 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 pages 9, 10, and 12.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil, 5 d/wk	0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil, 5 d/wk	0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil, 5 d/wk	0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil, 5 d/wk
Body weights in the 2-year study			
Dosed lower than vehicle controls	High dose lower than vehicle controls	High dose lower than vehicle controls	High dose lower than vehicle controls
Survival rates in the 2-year study			
35/50; 8/50; 1/50	34/50; 26/50; 11/50	39/49; 40/50; 28/50	41/50; 41/50; 38/50
Nonneoplastic effects			
Nephropathy and renal tubular cell hyperplasia	Mild nephropathy	None	None
Neoplastic effects			
Renal tubular cell adenomas or adenocarcinomas (combined) (0/50; 2/50; 5/50)	None	None	None
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	No evidence
Other considerations			
Poor survival reduced sensitivity of study	Poor survival reduced sensitivity of high dose group		

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 α-Methylbenzyl Alcohol is based on 13-week studies that began in May 1980 and ended in August 1980 and on 2-year studies that began in April 1981 and ended in April 1983 at Microbiological Associates (Bethesda, MD).

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PEER REVIEW PANEL (March 13, 1989)

The members of the Peer Review Panel who evaluated the draft Technical Report on α-methylbenzyl alcohol on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF α-METHYLBENZYL ALCOHOL (March 13, 1989)

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of α-methylbenzyl alcohol received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. M.P. Dieter, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats, no evidence of carcinogenic activity for female rats, no evidence of carcinogenic activity for male and female mice).

Dr. McKnight, a principal reviewer, stated that her main concern was the large number of purportedly accidental gavage-related deaths in rats. These apparent dose-related deaths raised questions about whether the animals in the different dose groups were treated differently, apart from the chemical effect. She said that if the "accidental" deaths were not a result of toxic effects of the chemical, then more explanation should be provided as to why the frequency of death increased so clearly with dose.

Dr. Gold, the second principal reviewer, agreed with the conclusion for male rats in principle but wanted more discussion about the severity of nephropathy and incidence of hyperplasia in the animals with adenomas and adenocarcinomas and how these nonneoplastic lesions compared with those in animals without such tumors. Dr. Dieter reported that four male rats in the low dose group and four in the high dose group had tubular cell hyperplasia and none had tubular cell tumors. Of the seven animals with tumors, none had hyperplasia, whereas all had marked severity for nephropathy. Dr. Gold also thought that the rat studies might be considered inadequate because of the large number of accidental deaths and poor survival. She asked for a description of NTP policy on maintaining a dose level throughout a study rather than reducing the dose when there are survival problems. Dr. J. Huff, NIEHS, stated that there is no set policy on changing exposure concentrations during the studies. Since the chemical is a food flavoring agent, Dr. Gold questioned why corn oil gavage, rather than feed, was chosen as the route of administration. Dr. Dieter said that the chemical was not stable in feed, that a high enough concentration could not be obtained in water, and that microencapsulation would be the route of choice today.

Dr. Lijinsky, the third principal reviewer, said that the studies were conducted with less than typical adequacy and that comments should be added about the nature of the gavage errors and how many deaths in each group were gavage related. If gavage-related deaths were too numerous, then consideration should be given to repeating the studies. He thought that the confusion over the numbers of accidental deaths made it difficult to assess whether the top doses in rats were optimal doses.

Dr. Dieter said that the apparent deaths resulting from the gavage technique did not appear to be random and that a cluster of accidents occurred between weeks 48 and 53 of the studies. There was a similar pattern of early mortality in the benzyl alcohol studies (NTP TR 343), which were conducted in the same laboratory. Dr. S. Eustis, NIEHS, added that the deaths were not due to simple mechanical trauma; i.e., there were no indications that gavage needles punctured the esophagus or trachea or that material was deposited directly in the lung for any of these deaths. The material in the lung resembled aspirated stomach contents. Dr. Huff commented that animals in gavage studies often quickly become aware of and anxious about receiving the chemical, whereas vehicle controls seem to be less so. Dr. Ashby further speculated that the smell or irritant properties along with a depressant

effect of the chemical could have contributed to the animals' being more difficult to handle, leading to greater difficulty in administering the mixture and, hence, to a greater likelihood of gavage error. As for the decision to continue the studies in rats, Dr. Dieter noted that there was reasonable survival in all groups through week 80; a steady and increasing rate of mortality ensued after that time. The NTP staff decided that the neoplastic effects were of major importance despite markedly reduced survival, and although the studies had these flaws, the increases in chemically induced neoplasms could not be discounted. Dr. Dieter stated that the later mortality was primarily due to a combination of nephropathy and chemical toxicity.

Dr. McKnight moved that the conclusion for male rats be changed to inadequate study of carcinogenic activity. Dr. Lijinsky seconded the motion, which was rejected by five panelists (Drs. Ashby, Garman, Klaassen, Perera, and Popp) to four (Drs. Gold, Lijinsky, McKnight, and Newberne), with one abstention (Dr. Gallo). Dr. Garman moved that the conclusion for male rats be accepted as written, some evidence of carcinogenic activity, with reservations concerning poor survival as written. Dr. Perera seconded the motion. Dr. Ashby moved to amend the motion to change the conclusion to equivocal evidence of carcinogenic activity; this was tabled for lack of a second. Dr. Garman's motion was rejected by five negative votes (Drs. Ashby, Gold, Lijinsky, McKnight, and Newberne) to three affirmative votes (Drs. Garman, Perera, and Popp), with two abstentions (Drs. Gallo and Klaassen).

In further discussion, most Panel members agreed that the tumor response in male rats was likely associated with chemical administration but considered the study in male rats to be confounded due to technical errors. Dr. Huff thought that the effects of gavage were receiving disproportionate attention and urged that this issue not affect consideration of other aspects of the studies. He asked the Panel if they indeed believed that, in order to address public health concerns, the male rat study should be repeated. Unconvinced, Dr. Klaassen made a motion to change the conclusion for male rats to inadequate study of carcinogenic activity. Dr. Ashby seconded the motion, which was accepted by six votes (Drs. Ashby, Gold, Klaassen, Lijinsky, McKnight, and Newberne) to three (Drs. Garman, Perera, and Popp), with one abstention (Dr. Gallo). Dr. Klaassen moved that the conclusions be accepted as written for female rats and male and female mice, no evidence of carcinogenic activity. Dr. Popp seconded the motion, which was accepted by nine panelists, with one abstention (Dr. Gallo). In discussion following this vote, questions were raised about the inconsistency of judging the study in female rats adequate when there was similarly poor survival, also likely due to gavage technique. Dr. Klaassen moved that the conclusion for female rats be changed to inadequate study of carcinogenic activity. Dr. Newberne seconded the motion, which was accepted by four votes (Drs. Ashby, Klaassen, Lijinsky, and Newberne) to two (Drs. Garman and Perera), with four abstentions (Drs. Gallo, Gold, McKnight, and Popp).

Dr. Scala asked Dr. Ashby to draft a statement that would convey to the NTP a sense of why a majority of the members of the Panel deemed the studies of α-methylbenzyl alcohol in rats to be inadequate. Such a statement was drafted, approved by the members of the Panel present on the day following the meeting, and presented to the NTP for action. The statement recommended that the NTP review the technical conduct of the studies in rats with two possible outcomes: (1) if the review confirms the technical adequacy of the overall study procedures, the levels of evidence as originally written in the report should be affirmed; or (2) if the NTP concludes that the rat studies were flawed, then the studies should be reclassified as inadequate and repeat studies should be considered.

PEER REVIEW PANEL (June 27, 1989)

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

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF α-METHYLBENZYL ALCOHOL (June 27, 1989)

At the peer review meeting on June 27, 1989, Dr. S. Eustis, NIEHS, began with a general discussion of the problem of deaths resulting from poor gavage technique and how to determine whether gavage was a factor in an animal's death. Speaking to the α-methylbenzyl alcohol studies, Dr. Eustis reported that dosing records, temperature and humidity data, clinical observations, and individual animal data records were reviewed by the study scientist, Dr. Dieter (NIEHS), and by the pathology staff. In addition, pathology diagnoses and slides from all early-death animals were re-examined to determine as accurately as possible the causes of death. This review revealed no evidence that environmental conditions, infectious disease, or other previously unreported factors contributed to the lowered survival in low and high dose male rats and high dose female rats. The majority of the early deaths recorded as accidental were associated with evidence that gavage was a factor. Review of the pathology data and slides confirmed that the preponderance of early deaths in dosed male rats could be attributed to exacerbation of chronic nephropathy by the chemical. In female rats, reduced survival in the high dose group seemed to be due primarily to the gavage-related deaths. In summary, Dr. Eustis stated that, after reviewing all pertinent clinical records and audit reports on these studies, the staff believed that the conduct of the studies was technically adequate.

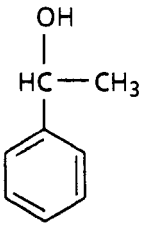
Dr. Eustis then described further investigations of the kidney in male rats. To aid in the interpretation of the pathology data, three additional sections from each animal were taken, which showed additional tubular cell neoplasms in low and high dose male rats. The incidences of tubular cell neoplasms found during the original evaluation of one section per kidney were as follows: vehicle control, 0/50; low dose, 2/50; and high dose, 5/50. The overall incidences of tubular cell neoplasms observed in the original evaluation and the additional sections combined were 1/50, 13/50, and 14/50. The increased tumor incidences were significant ($P<0.001$) in both the low and high dose groups compared with those in the vehicle controls.

Dr. Scala commented that, unless the Panel or the NTP wanted to recommend changing the level of evidence in male rats, no further action was required; however, he thought that a motion reflecting a sense of the Panel would be appropriate for the record. Dr. Popp moved that, based on the additional studies and evaluation conducted by the NTP and on the report presented by Dr. Eustis, the previously raised questions concerning the conduct of the studies were now answered to the satisfaction of the Panel; furthermore, the original levels of evidence, some evidence of carcinogenic activity for male rats and no evidence of carcinogenic activity for female rats, were still appropriate. Dr. Lijinsky seconded the motion. After further discussion, Dr. Mirer offered an amendment intended to confine the sense of the motion to the conduct of the study by deleting the sentence concerning the levels of evidence. Dr. Gold seconded the amendment, which was accepted unanimously. Dr. Popp's motion, minus the deleted sentence, was then accepted unanimously.

Dr. Scala concluded the review of α-methylbenzyl alcohol by noting that if the NTP intends to change the level of evidence for male rats, such a recommendation should be brought back to the Panel for evaluation.

I. INTRODUCTION

I. INTRODUCTION



α-METHYLBENZYL ALCOHOL

CAS No. 98-85-1

$C_8H_{10}O$ Molecular weight 122.2

Synonyms: Styrallyl alcohol; styralyl alcohol; α-methylbenzenemethanol; phenylmethylcarbinol; 1-phenethyl alcohol

Physical Properties and Purity

α-Methylbenzyl alcohol is a colorless compound that is a liquid at room temperature and a solid below 21° C. It exists as two optically active isomers; the commercial product is composed of the racemic mixture. The chemical is insoluble in water, miscible in diethyl ether and ethanol, and soluble in most other organic solvents (Fenaroli, 1975). α-Methylbenzyl alcohol has a boiling point of 204° C, a melting point of 20.7° C, a specific gravity of 1.0129, and an index of refraction of 1.5272 at 20° C (Condensed Chemical Dictionary, 1981). Food-grade α-methylbenzyl alcohol was obtained from Givaudan Corporation in two lots. Cumulative data indicated that both lots were greater than 99% pure; the first lot was tested for and met Food Chemical Codex specifications for assay, total ketone impurities, specific gravity, and refractive index.

Production, Use, and Exposure

α-Methylbenzyl alcohol is coproduced with propylene oxide by reaction of α-peroxyethylbenzene (formed by oxidation of ethyl benzene) with propylene (Kirk-Othmer, 1982).

There were only two domestic sources of α-methylbenzyl alcohol reported in 1977, with production levels of 100-500 million pounds; 10,000-100,000 pounds was imported (USEPA, 1988).

α-Methylbenzyl alcohol is used in cosmetics such as perfumes, creams, and soaps as a fragrance additive and is an intermediate in styrene production. This chemical is also added to foods as a flavoring agent and has been measured in nonalcoholic beverages, ice creams, ices, candy, baked goods, gelatins and puddings, and chewing gums at concentrations ranging between 0.3 and 9.0 ppm (Opdyke, 1974; Fenaroli, 1975). α-Methylbenzyl alcohol has been detected at low concentrations (1.7×10^{-5} g/liter) in river water (Rosen et al., 1963) and was qualitatively detected in finished drinking water samples by two Environmental Protection Agency laboratories (Shackelford and Keith, 1976; USEPA, 1976). Over 14,000 workers were potentially exposed to α-methylbenzyl alcohol between 1981 and 1983 (NIOSH, 1988).

Short-Term Toxicity

α-Methylbenzyl alcohol was an irritant in rabbits at a dermal dose of 10 mg per 24 hours (Smyth and Carpenter, 1944), caused moderately irritant effects to the skin at a dose of 500 mg per 24 hours (Opdyke, 1974), and severe effects to the eyes at a dose of 2 mg (Carpenter and Smyth, 1946). There were reports that provided estimates for an oral LD_{50} of 400 mg/kg in rats (Smyth and Carpenter, 1944), a subcutaneous LD_{50} of 250 mg/kg in mice (Rohrbach and Robineau, 1958), an intravenous LD_{Lo} of 200 mg/kg in dogs (Hjort and Kaufmann, 1920), and a percutaneous LD_{50} of greater than 2,500 mg/kg in rabbits (Opdyke, 1974).

Reproductive Toxicity

Dermal studies with female CrL:COBS CD (SD) BR strain rats were conducted at doses of 0, 0.14, 0.43, or 1.40 ml/kg per day during days 6-15 of pregnancy (USEPA, 1986). Clinical signs of toxicity were observed in the high dose group, and 3/35 animals died by day 20 of pregnancy. The remaining animals were killed. Body weight gain was decreased, leukocyte counts were increased, and clinicopathologic evidence of hepatotoxicity was present in dosed animals. α-Methylbenzyl alcohol exposure caused an increased incidence of embryo-fetal deaths, primarily early in pregnancy, and a decrease in litter size and weight. In addition, increased incidences of teratologic defects were observed, including anophthalmia and microphthalmia, ventricular septal defects, defects and irregularities affecting the thorax, kinky tail, defects of the thoracic ribs, and occurrence of cervical rib(s). No effects on liver or kidney weights were seen. The compound at the low and mid doses did not affect maternal toxicity or reproductive toxicity.

Absorption, Distribution, and Metabolism

A single oral dose of 460 mg/kg α-methylbenzyl alcohol was rapidly excreted by rabbits, with 82% of the dose appearing as urinary metabolites within 24 hours. Fifty percent of the material was α-methylbenzyl alcohol glucuronide, 30% was hippuric acid, and 1%-2% was mandelic acid (Smith et al., 1954). Rats excreted a small amount of a subcutaneous dose of methylbenzyl alcohol (0.15%) as acetophenone in urine (Hopkins et al., 1972). Rats displayed substrate stereoselectivity in the metabolism of racemic mixtures of α-methylbenzyl alcohol, excreting the R (+) isomer largely as the glucuronide, whereas the S (−) isomer underwent further oxidative metabolism (Testa and Jenner, 1976).

Genetic Toxicity

Few mutagenicity data are available for α-methylbenzyl alcohol. It did not cause growth inhibition due to DNA damage in two strains of *Escherichia coli* exposed to 50 µl/plate without S9 metabolic activation (Fluck et al., 1976). Zeiger et al. (1987) reported no induction of gene reversion by α-methylbenzyl alcohol in four strains of Salmonella treated according to a preincubation protocol with up to 6,666 µl/plate, with and without S9 (see Appendix H). Kojima et al. (1976) reported the induction of petite colony mutants of *Saccharomyces sake* after they were exposed to 0.20% α-methylbenzyl alcohol.

Mutagenicity information is available for three metabolites of α-methylbenzyl alcohol identified by Hopkins et al. (1972): acetophenone, mandelic acid, and hippuric acid. All test results were negative for these three metabolites, including assays for DNA damage in *E. coli* and *Bacillus subtilis* (Fluck et al., 1976; Kikuchi et al., 1977; Oda et al., 1978) and gene reversion in *Salmonella typhimurium* (Commoner, 1976; Milvy and Garro, 1976; Kikuchi et al., 1977; Florin et al., 1980; Elliger et al., 1984; Nohmi et al., 1985). No tests for genetic effects of these metabolites in higher organisms have been reported.

Carcinogenicity

There were no references to human or animal carcinogenicity data for α-methylbenzyl alcohol per se. However, α-methylbenzyl alcohol is a member of the benzylic acid series and has potential alkylating ability based on the benzyl carbonium ion.

Study Rationale

α-Methylbenzyl alcohol was nominated by the National Cancer Institute for study as a representative of the class of benzyl alcohols because there was limited toxicity information for these, because of their potential for mutagenicity or carcinogenicity based on chemical structure, and because several benzyl alcohols, including α-methylbenzyl alcohol, have been identified in drinking water.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF α-METHYLBENZYL ALCOHOL

CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

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Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF α-METHYLBENZYL ALCOHOL

Food-grade α-methylbenzyl alcohol was obtained as a colorless liquid in two lots from Givaudan Corporation (Clifton, NJ). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G).

The study chemical was identified by the analytical chemistry laboratory as α-methylbenzyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Both lots of α-methylbenzyl alcohol were found be be greater than 99% pure, as determined by elemental analysis, Karl Fischer water analysis, determination of ketone concentration by reaction of the study material with an alkaline solution of hydroxylamine hydrochloride followed by back-titration with 0.1 N or 0.5 N hydrochloric acid, thin-layer chromatography, and gas chromatography.

The identity of the study chemical at the study laboratory was confirmed by infrared spectroscopy. The stability of the study chemical was monitored by gas chromatography. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

α-Methylbenzyl alcohol dissolved in corn oil at 4.96 mg/ml or 150 mg/ml was found by gas chromatography to be stable for at least 14 days when stored at room temperature. Dose mixtures at 75 mg/ml were found be be stable for at least 21 days when stored at 5° C. Dose mixtures were stored no longer than 15 days at 4° C for the 13-week studies and no longer than 3 weeks at 5° C for the 2-year studies.

Periodic analysis of formulated α-methylbenzyl alcohol mixtures was conducted at the study laboratory and at the analytical chemistry laboratory by gas chromatography. Dose mixtures were analyzed one time during the 13-week studies. The results of the analysis indicated that all doses were within ±1% of the target concentrations.

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the α-methylbenzyl alcohol studies, dose analyses were conducted 13-15 times at 1- to 2-month intervals throughout the studies and all the mixtures were formulated within ±10% of the target concentrations (Table G4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table G5).

SINGLE-ADMINISTRATION STUDIES

A single-administration study was conducted at a dose range of 50-800 mg/kg; one female mouse in the highest dose group, 800 mg/kg, died. The data were insufficient for dose selection for the 16-day studies, and the single-administration studies were repeated at higher doses. The second study is the one presented in this report.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 14 days before the studies began. Groups of five rats and five mice of each sex were fasted overnight and then administered a single dose of 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg α-methylbenzyl alcohol in corn oil by gavage. Animals were weighed at the start and end of the studies. Animals were observed two times per day for 14 days. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 1.

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 13 days (rats) and 14 days (mice) before the studies began. The rats were 6-7 weeks old when placed on study, and the mice were 6-8 weeks old.

Groups of five rats and four or five mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg α-methylbenzyl alcohol in corn oil by gavage, 5 days per week for 12 doses over 16 days.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	4 or 5 males and 5 females of each species	10 males and 10 females of each species	49 or 50 males and 50 females of each species
Doses			
0, 313, 625, 1,250, 2,500, or 5,000 mg/kg α-methylbenzyl alcohol in corn oil by gavage; dose vol--10 ml/kg	0, 125, 250, 500, 1,000, or 2,000 mg/kg α-methylbenzyl alcohol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 93, 187, 375, 750, or 1,500 mg/kg α-methylbenzyl alcohol in corn oil by gavage; mice--0, 46.9, 93.8, 187.5, 375, or 750 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose			
11/7/79	Rats--2/5/80; mice--2/6/80	5/19/80	Rats--4/27/81; mice--4/6/81
Date of Last Dose			
N/A	Rats--2/20/80; mice--2/21/80	8/15/80	Rats--4/15/83; mice--3/25/83
Duration of Dosing			
Single dose	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 at the end of the studies	Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 16-d studies	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and then at least 1 × mo
Necropsy and Histologic Examinations			
Necropsy performed on all animals	Necropsy performed on all animals; histologic exams performed on 2 male and 2 female rats in the 1,000 mg/kg groups, 2 male and 2 female mice in the 500 mg/kg groups, and 1 male and 1 female of each species in the vehicle control groups	Necropsy performed on all animals; tissues examined histologically for vehicle control and highest dose groups and for all animals dying before the end of the studies. Spleen examined for all rats receiving 750 mg/kg and male rats receiving 375 mg/kg. Liver weighed at necropsy	Necropsy and histologic exams performed on all rats, all male mice, vehicle control and high dose female mice, and low dose female mice with gross lesions or that died before the end of the study; the following tissues were examined: adrenal glands, brain, duodenum, esophagus, femur including marrow, gallbladder (mice), gross lesions, heart, kidneys, large intestine, larynx or anterior trachea, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, mesenteric lymph nodes (mice), nasal turbinates, ovaries or testes, pancreas, parathyroids, pituitary gland, preputial or clitoral gland, prostate or uterus, salivary glands, skin, spleen, stomach, thymus (mice), thyroid gland, and urinary bladder. Tissues examined for low dose female mice: stomach and uterus
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	F344/N rats; $B6C3F_1$ mice

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animal Source Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory Microbiological Associates	Microbiological Associates	Microbiological Associates	Microbiological Associates
Method of Animal Identification Ear punch	Ear clip	Ear clip	Ear tag
Time Held Before Study 14 d	Rats--13 d; mice--14 d	19 d	Rats--19 d; mice--26 d
Age When Placed on Study Rats--6-7 wk; mice--6-8 wk	Rats--6-7 wk; mice--6-8 wk	Rats--7-8 wk; mice--8-9 wk	Rats--7-8 wk; mice--9-10 wk
Age When Killed Rats--8-9 wk; mice--8-10 wk	Rats--8-9 wk; mice--8-10 wk	Rats--20-21 wk; mice--21-22 wk	Rats--112-113 wk; mice--113-114 wk
Necropsy Dates 11/21/79	Rats--2/21/80; mice--2/22/80	Rats--8/18/80-8/19/80; mice--8/19/80-8/20/80	Rats--4/25/83-4/27/83; mice--4/4/83-4/6/83
Method of Animal Distribution Animals distributed to weight classes and then assigned to cages and to groups by a table of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Diet Purina Lab Block® (Ralston Purina, Richmond, IN); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies
Bedding Hardwood chips (P.J. Murphy, Co., Moonachie, NJ)	Hardwood chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)	Same as 16-d studies	Same as 16-d studies
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages Polycarbonate (Lab Products, Inc., or Hazleton Systems, Inc., Aberdeen, MD)	Polycarbonate (Lab Products, Inc., Rochelle Park, NJ, or Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-d studies	Same as 16-d studies
Cage Filters Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage 5	5	5	5

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--58°-76° F; hum--55%-70%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--52°-89° F; hum--40%-70%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--74° ± 2° F; hum--50% ± 10%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--66°-86° F; hum--22%-80%; fluorescent light 12 h/d; 12-15 room air changes/h

Five animals were housed per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on day 1, after 1 week, and at the end of the studies. Details of animal maintenance are presented in Table 1. A necropsy was performed on all animals. Histologic examinations were performed on two male and two female rats in the 1,000 mg/kg groups, two male and two female mice in the 500 mg/kg groups, and one male and one female of each species in the vehicle control groups.

THIRTEEN-WEEK STUDIES

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

Four- to five-week-old male and female F344/N rats and 5- to 6-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 19 days, and then assigned to cages and groups according to a table of random numbers. Rats were 7-8 weeks old when placed on study, and mice were 8-9 weeks old.

Groups of 10 rats of each sex were administered 0, 93, 187, 375, 750, or 1,500 mg/kg α-methylbenzyl alcohol in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 46.9, 93.8, 187.5, 375, or 750 mg/kg on the same schedule.

Animals were observed two times per day. Individual animal weights were recorded one time per week. Further experimental details are summarized in Table 1.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. The liver was weighed at necropsy. Histologic examinations were performed on all animals in the vehicle control groups, on male and female rats in the 1,500 mg/kg groups, on male and female mice in the 750 mg/kg groups, and on all animals that died before the end of the studies. The spleen was examined for male and female rats in the 750 mg/kg groups and for male rats in the 375 mg/kg group. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 49 or 50 mice of each sex were administered 0, 375, or 750 mg/kg α-methylbenzyl alcohol in corn oil by gavage, 5 days per week for 103 weeks.

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. 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. Animals were shipped to the study laboratory at 4-5 weeks (rats) or 5-6 weeks (mice) of age. Rats were quarantined at the study laboratory for 19 days and mice for 26 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7-8 weeks of age and the mice at 9-10 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the National Toxicology Program (NTP) Sentinel Animal Program (Appendix E).

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 an NTP 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 one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/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 are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. Cages were not rotated during the studies. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded one time per week for the first 12 weeks of the study and at least one time 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 missexed. Some tissues were excessively autolyzed or cannibalized, and thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) 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. Mortality in the highest dose group exceeded that in the vehicle control group by 15%, so complete histopathologic examinations were performed on all rats in the low dose group in addition to those in the high dose group.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Carcinogenesis Bioassay Data System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness

of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle. Potential target organs selected for review were the kidney, nasal cavity, and salivary gland for male rats, kidney and spleen for female rats, and forestomach for mice.

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

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be 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 each dosed group 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

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SINGLE-ADMINISTRATION STUDIES

All rats that received 2,500 or 5,000 mg/kg and 1/5 male rats that received 1,250 mg/kg died within 4 days after dosing (Table 2). On the day of dosing, rats that received 625 mg/kg or more were ataxic or lethargic. All survivors were normal from day 4 to the end of the studies. Final mean body weights were not related to the dose administered.

SIXTEEN-DAY STUDIES

Two of five male rats and 4/5 female rats that received 2,000 mg/kg died before the end of the studies (Table 3). The final mean body weights of rats that received 500, 1,000, or 2,000 were 5%, 7%, or 21% lower than that of the vehicle controls for males and 8%, 7%, or 15% lower for females. One male and one female rat that received 2,000 mg/kg exhibited labored breathing and were lethargic after dosing. Hemorrhagic gastrointestinal tracts were observed in one female and two male rats in this dose group. No compound-related histopathologic lesions were observed in two male and two female rats dosed at 1,000 mg/kg.

THIRTEEN-WEEK STUDIES

Deaths of 1/10 male rats and 3/10 female rats that received 1,500 mg/kg were considered to be

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF α-METHYLBENZYL 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	140 ± 0	221 ± 9	+81 ± 9	
313	5/5	135 ± 3	201 ± 4	+66 ± 2	91
625	5/5	139 ± 10	203 ± 9	+64 ± 4	92
1,250	(d) 4/5	143 ± 8	212 ± 8	+65 ± 14	96
2,500	(e) 0/5	143 ± 13	(f)	(f)	(f)
5,000	(g) 0/5	135 ± 5	(f)	(f)	(f)
FEMALE					
0	5/5	109 ± 4	141 ± 4	+32 ± 2	
313	5/5	114 ± 2	141 ± 4	+27 ± 2	100
625	5/5	114 ± 10	140 ± 3	+26 ± 6	99
1,250	5/5	107 ± 2	138 ± 1	+31 ± 3	98
2,500	(h) 0/5	108 ± 4	(f)	(f)	(f)
5,000	(g) 0/5	106 ± 4	(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 weight change of the survivors ± standard error of the mean
(d) Day of death: 1
(e) Day of death: 1,1,1,1,4
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: all 1
(h) Day of death: 1,1,2,2,3

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF α-METHYLBENZYL 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	108 ± 3	191 ± 5	+83 ± 4	
125	5/5	108 ± 4	186 ± 4	+78 ± 3	97
250	5/5	112 ± 5	186 ± 6	+74 ± 2	97
500	5/5	110 ± 3	181 ± 1	+71 ± 3	95
1,000	5/5	110 ± 4	178 ± 4	+68 ± 3	93
2,000	(d) 3/5	108 ± 6	151 ± 7	+42 ± 8	79
FEMALE					
0	5/5	98 ± 3	142 ± 3	+44 ± 3	
125	5/5	94 ± 2	135 ± 2	+41 ± 2	95
250	5/5	91 ± 3	135 ± 4	+44 ± 2	95
500	5/5	95 ± 1	130 ± 2	+35 ± 1	92
1,000	5/5	96 ± 2	132 ± 4	+36 ± 3	93
2,000	(e) 1/5	95 ± 3	120	+20	85

(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: 2,2
(e) Day of death: 1,1,2,15

compound related (Table 4). Other deaths were described as being related to the gavage procedure. The final mean body weight of rats that received 1,500 mg/kg was 12% lower than that of vehicle controls for males and 7% lower for females. Throughout the studies, rats that received 750 or 1,500 mg/kg exhibited ataxia, rapid breathing, and lethargy for up to 30 minutes after dosing; after 30 minutes, these clinical signs subsided. The liver weight to body weight ratios for male rats in the 375, 750, and 1,500 mg/kg groups and for all dosed female groups were significantly greater than those for vehicle controls (Table 5). A minimal-to-mild increase in brown pigment, characteristic of hemosiderin, was seen in macrophages in the spleen of 10/10 males receiving 750 mg/kg and 9/10 males receiving 1,500 mg/kg, but none was seen in males receiving 375 mg/kg. A similar pigment was seen in the spleen of 6/10 females receiving 1,500 mg/kg, but none was seen in females receiving 750 mg/kg. All 10 serum samples from vehicle control rats had positive titers against rat coronavirus.

Dose Selection Rationale: Because there were no deaths or life-threatening histopathologic lesions attributed to α-methylbenzyl alcohol at 375 or 750 mg/kg, these doses were selected for male and female rats for the 2-year studies, administered in corn oil by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 4%-11% lower than those of vehicle controls from week 3 to week 56 and 12%-32% lower thereafter (Table 6 and Figure 1). Mean body weights of low dose male rats were 10%-20% lower than those of vehicle controls from week 93 to the end of the study. Mean body weights of high dose female rats were 6%-10% lower than those of vehicle controls from week 16 to week 44 and 12%-19% lower thereafter. Mean body weights of low dose and vehicle control female rats were similar. Male and female rats were lethargic for a short time after they were dosed.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF α-METHYLBENZYL 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	180 ± 4	359 ± 5	+179 ± 6	
93	10/10	178 ± 3	361 ± 8	+183 ± 5	101
187	10/10	170 ± 3	355 ± 5	+185 ± 6	99
375	10/10	176 ± 3	338 ± 8	+162 ± 7	94
750	9/10	180 ± 3	342 ± 4	+162 ± 4	95
1,500	(d) 7/10	178 ± 3	317 ± 8	+138 ± 8	88
FEMALE					
0	10/10	122 ± 2	213 ± 9	+91 ± 9	
93	9/10	123 ± 2	213 ± 5	+89 ± 3	100
187	9/10	123 ± 3	209 ± 4	+86 ± 5	98
375	9/10	117 ± 2	203 ± 3	+85 ± 1	95
750	8/10	118 ± 2	195 ± 4	+77 ± 4	92
1,500	(e) 6/10	125 ± 2	198 ± 6	+73 ± 6	93

(a) Number surviving/number initially in group; deaths at 750 mg/kg or less were related to gavage procedure.
(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: 1; the other two deaths were judged to be related to the gavage procedure.
(e) Week of death: 1,1,2; the other death was judged to be related to the gavage procedure.

TABLE 5. LIVER WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL (a)

Dose (mg/kg)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	363 ± 4.8	16,497 ± 618	45.5 ± 1.56
93	10	356 ± 7.5	16,551 ± 794	46.3 ± 1.55
187	10	356 ± 4.4	16,631 ± 587	46.7 ± 1.47
375	10	347 ± 5.9	18,089 ± 579	**52.0 ± 1.06
750	9	342 ± 4.9	17,979 ± 406	**52.5 ± 0.98
1,500	7	**323 ± 9.0	18,379 ± 564	**57.0 ± 1.24
FEMALE				
0	10	205 ± 3.5	7,755 ± 249	37.8 ± 1.06
93	9	214 ± 4.3	**9,279 ± 404	**43.3 ± 1.30
187	9	207 ± 4.0	8,746 ± 246	*42.4 ± 1.27
375	9	204 ± 2.2	*8,808 ± 117	**43.2 ± 0.59
750	8	199 ± 3.2	**9,549 ± 348	**48.0 ± 1.24
1,500	6	200 ± 5.6	**10,625 ± 281	**53.3 ± 0.73

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	375 mg/kg Av. Wt. (grams)	375 mg/kg Wt. (percent of veh. controls)	375 mg/kg No. of Survivors	750 mg/kg Av. Wt. (grams)	750 mg/kg Wt. (percent of veh. controls)	750 mg/kg No. of Survivors
MALE								
1	201	49	198	99	50	185	92	48
2	208	49	221	106	50	203	98	48
3	247	49	234	95	50	223	90	46
4	267	49	258	97	50	240	90	46
5	285	49	273	96	50	259	91	46
6	286	49	278	97	50	269	94	46
7	294	49	277	94	50	280	95	46
8	310	49	303	98	48	297	96	46
9	328	49	317	97	48	309	94	46
11	332	49	324	98	48	313	94	46
12	345	49	334	97	48	324	94	46
16	370	49	364	98	48	357	96	46
20	401	49	393	98	48	372	93	46
24	422	49	411	97	48	385	91	46
28	434	49	429	99	48	400	92	46
32	450	49	444	99	48	413	92	45
36	456	49	454	100	48	416	91	45
40	464	49	461	99	48	423	91	44
44	475	49	476	100	48	435	92	44
48	488	49	482	99	47	436	89	44
52	488	49	475	97	45	442	91	43
56	487	49	489	100	43	436	90	42
60	502	49	492	98	43	442	88	42
64	500	49	496	99	43	436	87	39
69	502	49	492	98	42	416	83	39
72	507	49	495	98	42	430	85	35
76	510	49	505	99	41	422	83	32
80	505	49	482	95	41	410	81	28
84	499	48	468	94	37	412	83	17
88	508	47	472	93	31	394	78	11
93	495	43	446	90	23	388	78	3
100	485	37	413	85	13	388	80	1
103	471	35	378	80	8	321	68	1
FEMALE								
1	141	50	142	101	50	136	96	47
2	152	50	161	106	50	146	96	46
3	164	50	163	99	50	149	91	46
4	169	50	168	99	50	165	98	46
5	176	50	175	99	50	170	97	46
6	179	50	177	99	50	170	95	45
7	185	50	182	98	50	176	95	45
8	190	50	189	99	50	184	97	45
9	194	50	192	99	50	186	96	45
11	197	50	196	99	50	189	96	45
12	204	50	199	98	50	197	97	45
16	215	50	210	98	50	203	94	45
20	225	50	217	96	50	209	93	45
24	231	50	224	97	50	214	93	45
28	238	50	230	97	50	218	92	45
32	243	50	238	98	50	224	92	45
36	242	50	243	100	50	224	93	45
40	250	49	247	99	50	224	90	44
44	259	49	256	99	50	233	90	42
48	269	49	263	98	50	235	87	39
52	274	49	268	98	46	241	88	36
56	284	49	278	98	45	240	85	32
60	295	49	290	98	45	249	84	32
64	302	49	292	97	45	253	84	29
69	310	48	291	94	45	262	85	28
72	319	48	311	97	44	264	83	28
76	318	47	311	98	43	266	84	28
80	321	44	319	99	43	271	84	27
84	319	44	315	99	42	280	88	23
88	321	44	318	99	39	271	84	22
93	328	41	317	97	35	272	83	19
100	332	37	322	97	29	272	82	13
103	334	35	320	96	27	271	81	11

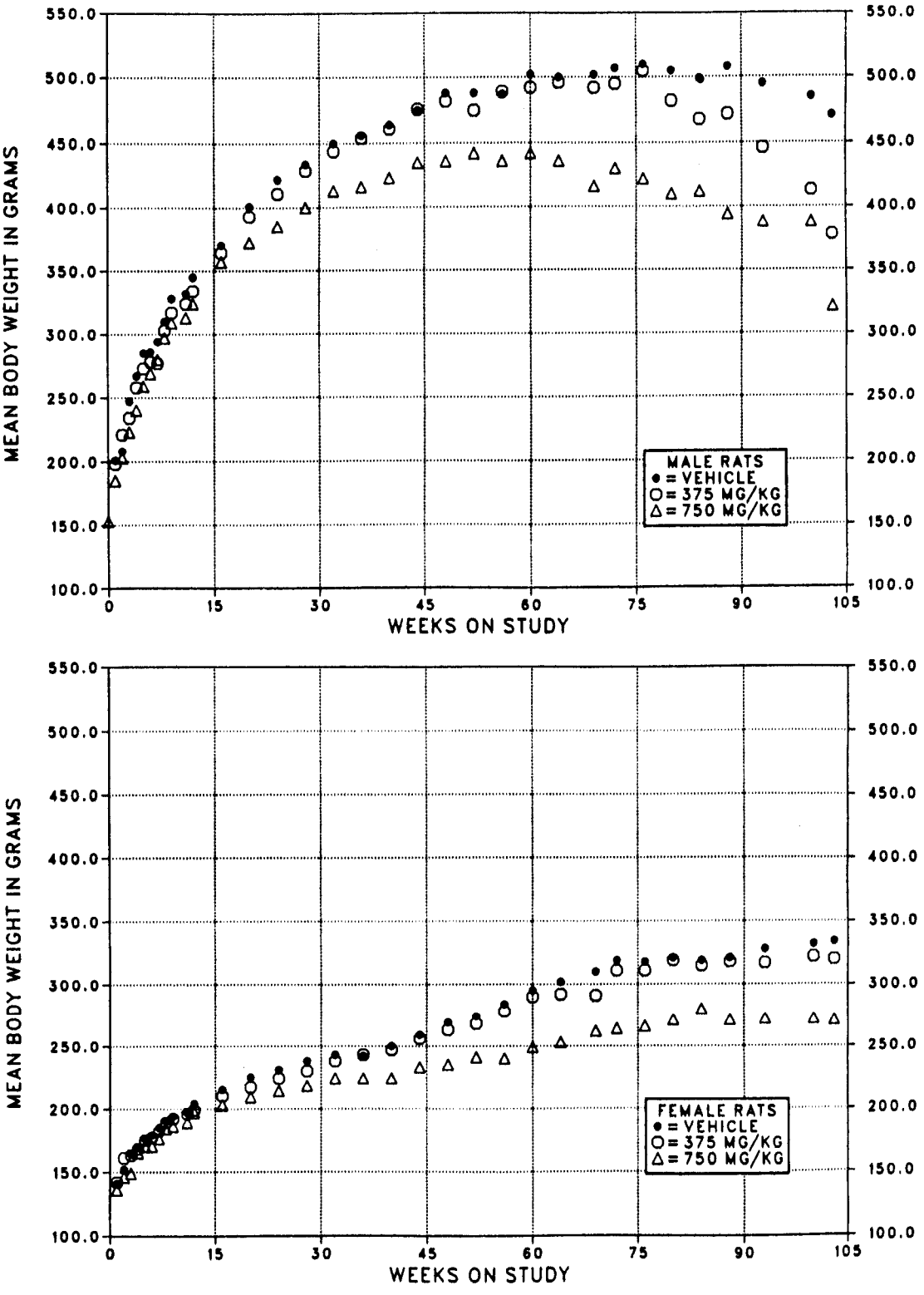

FIGURE 1. GROWTH CURVES FOR RATS EXPOSED TO α-METHYLBENZYL ALCOHOL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered α-methylbenzyl alcohol at the doses used in these studies and for vehicle controls are shown in Table 7 and in the Kaplan and Meier curves in Figure 2. The survival of both the low (after week 86) and the high (after week 65) dose groups of male rats was significantly lower than that of the vehicle controls. The survival of the high dose group of female rats was significantly lower than that of the vehicle controls after week 40. Because the deaths of 18 male and 19 female rats were judged to be accidental, survival curves that do not exclude any animals are presented for comparison in Figure 3.

The increased mortality in high dose females and part of that in dosed males is attributable to early deaths recorded as accidental. The majority of these were associated with convincing evidence that gavage was a major factor in the animals' deaths. This evidence included clinical observation of death shortly after gavage; evidence of the oil vehicle in the trachea, lungs, or thoracic cavity at necropsy; foreign body pneumonia or pleuritis; and/or perforation of the esophagus. During the standard audit procedures used by the National Toxicology Program (NTP) (see Audit Summary, Appendix I), these data were corroborated. In addition, the NTP study scientist and pathologists reviewed clinical observations, dosing records, temperature and humidity data, individual animal necropsy records, and tissue sections from all early-death animals to determine as accurately as possible the causes of death. This review revealed no evidence that environmental conditions, infectious disease, or other previously unreported factors contributed to the lower survival in low and high dose male rats and high dose female rats. The review of the pathology data and histologic slides also confirmed that the preponderance of early deaths in dosed male rats can be attributed to the exacerbation of spontaneous nephropathy by α-methylbenzyl alcohol (see page 34 and Table 8).

TABLE 7. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

	Vehicle Control	375 mg/kg	750 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	12	30	37
Moribund kills	2	3	4
Killed accidentally	1	9	8
Animals surviving until study termination	35	8	1
Survival P values (b)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	13	(c) 21	24
Moribund kills	2	0	1
Killed accidentally	1	4	14
Animals surviving until study termination	34	26	11
Survival P values (b)	<0.001	0.275	<0.001

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(c) One animal died during the termination period and was combined, for statistical purposes, with those killed at termination.

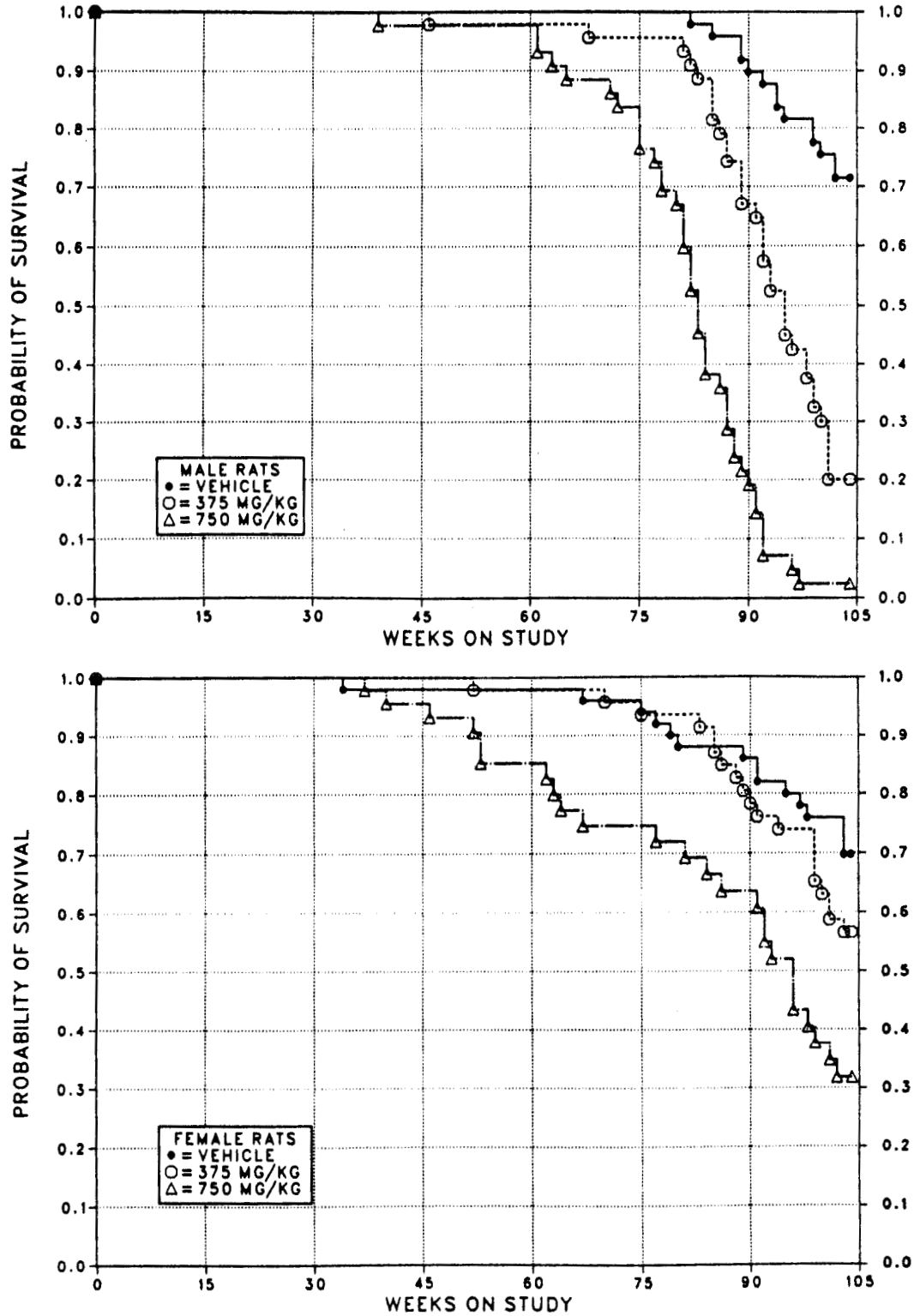

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO α-METHYLBENZYL ALCOHOL BY GAVAGE FOR TWO YEARS

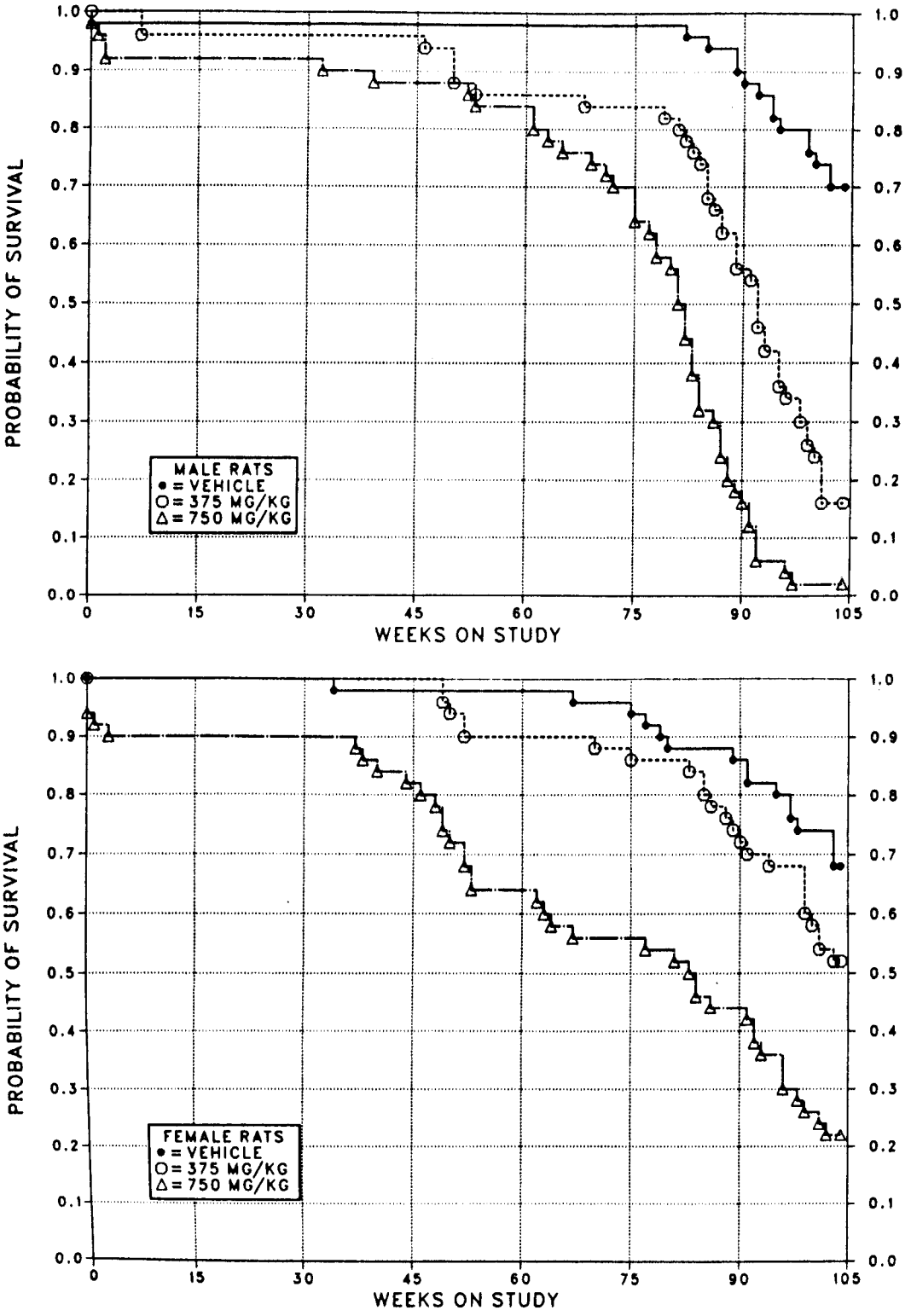

FIGURE 3. STANDARD SURVIVAL CURVES FOR RATS EXPOSED TO α-METHYLBENZYL ALCOHOL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, parathyroids, heart, glandular stomach, bone, urinary bladder, liver, forestomach, lung, nasal cavity, salivary gland, eye, and hematopoietic system.

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.

Kidney: Spontaneous nephropathy occurred in nearly all male and more than half of the female rats in all dosed groups and vehicle controls; however, this age-related renal disease was judged to be more severe in dosed male rats relative to vehicle controls (Table 8). Nephropathy was characterized by varied degrees of degeneration and regeneration of tubular epithelium, atrophy and dilation of some tubules, hyaline casts in the tubular lumina, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. Hyperplasia of the transitional epithelium overlying the renal pelvis was increased ($P<0.01$) in low dose male rats (male: vehicle control, 3/50; low dose, 20/50; high dose, 4/50; female: 1/50; 0/49; 0/50).

A single section of the left and right kidney of each rat was examined microscopically as a standard procedure during the histopathologic evaluation. With this procedure, tubular cell adenomas (Figures 4 and 5) were identified in low and high dose males but not in vehicle controls; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 9). A tubular cell adenocarcinoma occurred in one low dose male rat (Figures 6 and 7). One vehicle control female rat had an adenocarcinoma that was a metastatic neoplasm originating in the mammary gland (not a primary renal tubular cell adenocarcinoma).

Renal tubular cell neoplasms are often late-appearing neoplasms seen only during microscopic examination in 2-year-old rats (i.e., they are often not seen macroscopically at necropsy). All the tubular cell adenomas observed in the standard single sections of kidney from dosed male rats were identified only during the microsopic examination. Because the number of tubular cell neoplasms identified by the standard procedures in the dosed male rats was low, step-sections of kidney were made to clarify the potential relationship of these rare neoplasms to chemical administration. The remaining half of the right and left kidney from each male rat was embedded, and three or four additional step-sections were made at approximately 1-mm intervals. These were examined microscopically, and additional tubular cell neoplasms were identified (Table 10). The combined data (tubular cell lesions identified in standard single sections and step-sections) are shown in Table 11. The incidences of tubular cell neoplasms in the low and high dose male rats are statistically significant relative to those in vehicle controls.

Tubular cell hyperplasia, adenoma, and carcinoma occurred in the cortex of the kidney and appeared to encompass a morphologic continuum. Tubular cell hyperplasia generally was characterized by one or two cross-sections of a normal-to-slightly enlarged tubule with stratified epithelium that partially or completely occluded the tubular lumen. The cells were often enlarged and contained nuclei with prominent nucleoli. Adenomas were circumscribed masses of epithelial cells and were usually larger than the cross-sectional diameter of three tubules. The epithelium formed a solid sheet of cells within the mass or was arranged in packets separated by basement membrane. The cells were generally uniform in appearance with pale eosinophilic or basophilic cytoplasms and round nuclei with prominent nucleoli. The tubular cell adenocarcinoma was larger than the adenomas and exhibited a heterogenous growth pattern with some cellular pleomorphism or atypia. None of the carcinomas metastasized to other organs.

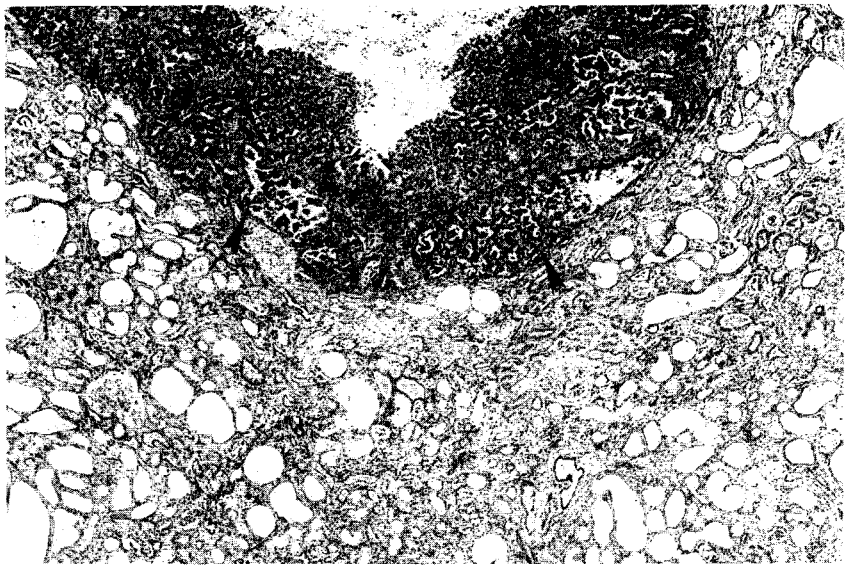

Figure 4. Renal tubular cell adenoma in high dose male rat no. C08. The boundary of the neoplasm is indicated by arrows. Note the dilated nephrons and interstitial connective tissue indicative of nephropathy (hematoxylin and eosin stain).

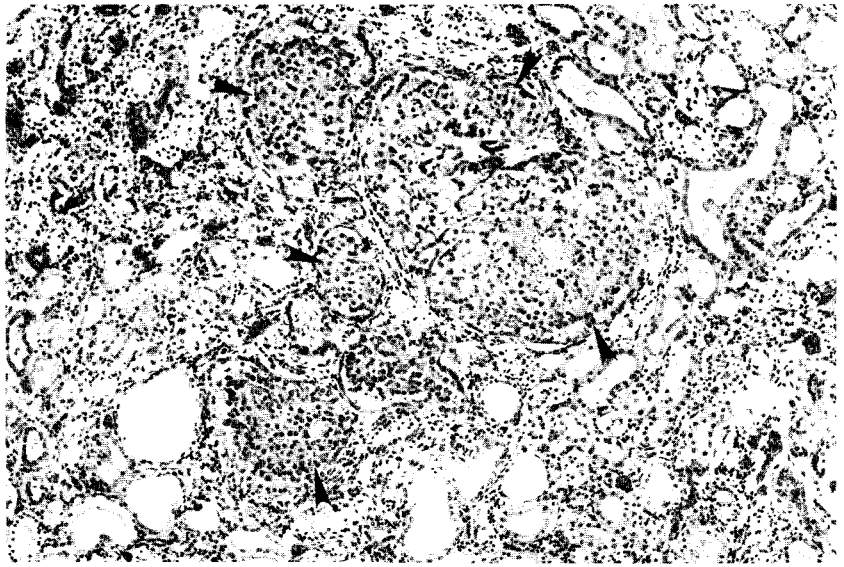

Figure 5. Renal tubular cell adenoma in high dose male rat no. C20. Note the nodular appearance, probably related to the convolutions of the affected nephron (hematoxylin and eosin stain).

Figure 6. Renal tubular cell adenocarcinoma in low dose male rat no. C17. The neoplasm is in the upper part of the photomicrograph, and the boundary with the normal renal parenchyma is indicated by arrows (hematoxylin and eosin stain).

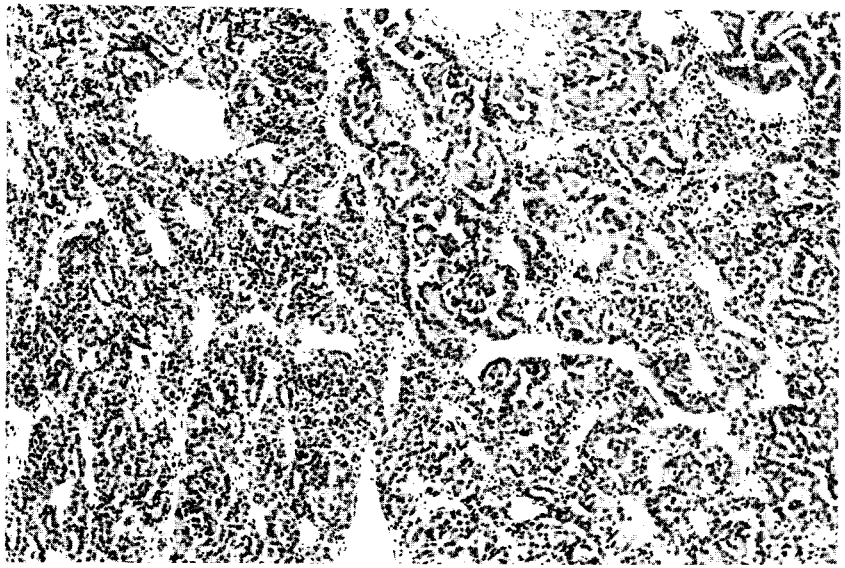

Figure 7. Higher magnification of renal tubular cell adenocarcinoma in low dose male rat no. C17. Note the variation in growth pattern and cellular pleomorphism (hematoxylin and eosin stain).

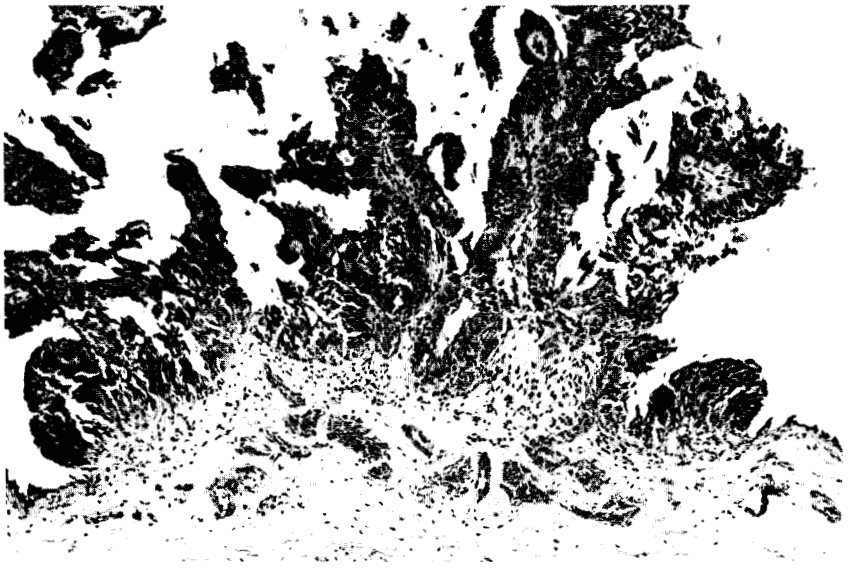

Figure 8. Transitional cell papilloma in the urinary bladder of high dose male rat no. C24. Note the multiple papillae consisting of thin connective tissue cores and the overlying transitional epithelium (hematoxylin and eosin stain).

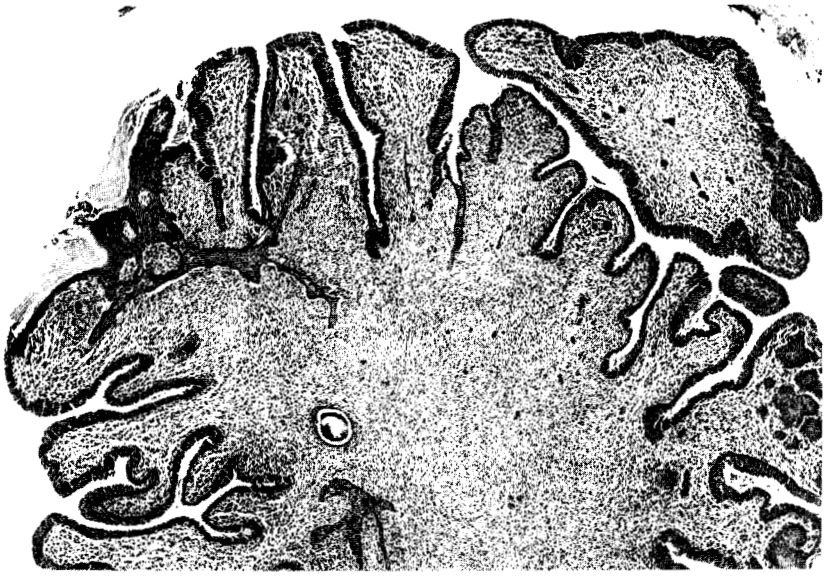

Figure 9. Transitional cell papilloma in the urinary bladder of high dose female rat no. C21. This papilloma is not typical in that it is composed predominantly of connective tissue with a relatively thin covering of transitional epithelium (hematoxylin and eosin stain).

TABLE 8. INCIDENCES AND SEVERITY OF NEPHROPATHY IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

	Vehicle Control	375 mg/kg	750 mg/kg
MALE			
Incidence	41/50 (82%)	47/50 (94%)	46/50 (92%)
Severity (a)			
Minimal	1	3	1
Mild	30	4	2
Moderate	9	7	10
Marked	1	33	33
Mean severity (b)	2.0	3.5	3.5
FEMALE			
Incidence	28/50 (56%)	39/49 (80%)	27/50 (54%)
Severity (a)			
Minimal	10	17	6
Mild	13	15	14
Moderate	4	6	6
Marked	1	1	1
Mean severity (b)	1.8	1.8	2.0

(a) Number of rats with indicated severity
(b) Grade of severity: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked.

TABLE 9. KIDNEY TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL (a)

	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	5/50 (10%)
Terminal Rates	0/35 (0%)	1/8 (13%)	1/1 (100%)
Week of First Observation		104	83
Incidental Tumor Test	P<0.001	P=0.210	P=0.010
Adenocarcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adenoma or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	2/50 (4%)	5/50 (10%)
Terminal Rates	0/35 (0%)	1/8 (13%)	1/1 (100%)
Week of First Observation		101	83
Incidental Tumor Test	P<0.001	P=0.141	P=0.010

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory: 0/148; historical incidence in NTP studies (mean ± SD): 11/2,092 (0.5% ± 0.9%)

TABLE 10. KIDNEY TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL: ADDITIONAL STEP-SECTIONS

Lesion	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia	1	3	3
Adenoma (single)	1	7	10
Adenoma (multiple)	0	4	0
Hyperplasia, oncocytic	0	0	1
Oncocytoma	0	2	1

TABLE 11. KIDNEY TUBULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL: COMPOSITE RESULTS

Lesion	Vehicle Control	375 mg/kg	750 mg/kg
Hyperplasia	1	7	6
Adenoma (single)	1	8	13
Adenoma (multiple)	0	4	1
Adenocarcinoma	0	1	0
Adenoma or adenocarcinoma (combined)	1	13	14
Effective number of animals (a)	49	41	28
Fisher exact test		P<0.001	P<0.001

(a) Number of animals alive at week 81 (time of occurrence of first tubular cell tumor in any group)

Parathyroids, Heart, Glandular Stomach, and Bone: Parathyroid hyperplasia, calcification of the heart and glandular stomach, and fibrous osteodystrophy of the bone were observed at markedly increased incidences in low dose male rats (Table 12). These changes were believed to be a secondary response stemming from a mineral imbalance caused by renal toxicity.

Urinary Bladder: Transitional cell papillomas were seen in 1/47 high dose male rats and in 2/48 high dose female rats (Figures 8 and 9). The historical incidence of transitional cell papillomas or carcinomas (combined) in corn oil vehicle control F344/N rats is 5/2,034 (0.2%) for males and 4/2,026 (0.2%) for females. The incidences of epithelial hyperplasia of the urinary bladder were not increased in dosed rats (male: vehicle control, 3/48; low dose, 4/46; high dose, 1/47; female: 0/49; 1/47; 0/48).

Liver: Centrilobular necrosis was observed at increased incidences ($P<0.01$) in dosed male rats (male: vehicle control, 0/50; low dose, 8/50; high dose, 8/50; female: 2/50; 0/48; 0/49).

Forestomach: Inflammation was observed at increased incidences ($P<0.05$) in dosed male rats (male: vehicle control, 4/49; low dose, 16/49; high dose, 11/47; female: 3/49; 1/48; 1/46).

Lung: Congestion was observed at increased incidences ($P<0.01$) in dosed female rats (male: vehicle control, 4/50; low dose, 8/50; high dose, 10/50; female: 5/50; 17/49; 23/48). Hemorrhage and foreign material were observed at increased incidences in high dose rats (hemorrhage--male: 0/50; 1/50; 5/50; $P<0.05$; female: 0/50; 0/49; 6/48; $P<0.05$; foreign material--male: 0/50; 2/50; 4/50; female: 0/50; 2/49; 8/48; $P<0.01$).

Nasal Cavity: Suppurative inflammation was observed at increased incidences ($P<0.01$) in dosed male rats (male: vehicle control, 7/47; low dose, 24/50; high dose, 30/50; female: 3/48; 2/48; 4/49).

Salivary Gland: Acute inflammation was observed at increased incidences ($P<0.01$) in dosed male rats (male: vehicle control, 1/49; low dose, 12/43; high dose, 9/39; female: 0/46; 1/49; 1/47).

TABLE 12. INCIDENCES OF SELECTED NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL

Site/Lesion	Vehicle Control	375 mg/kg	750 mg/kg
Parathyroid			
Hyperplasia	0/29	**23/37	4/35
Heart			
Calcification	1/50	**9/50	0/50
Glandular Stomach			
Calcification	1/49	*8/49	3/47
Bone			
Fibrous osteodystrophy	1/50	**21/50	*7/50

*P<0.05 vs. vehicle controls
**P<0.01 vs. vehicle controls

Eye: Cataracts were observed at increased incidences (P<0.01) in low dose rats (male: vehicle control, 2/50; low dose, 11/50; high dose, 2/50; female: 0/50; 13/50; 4/50).

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with significant negative trends (Tables A3 and B3); the incidences in the dosed groups were significantly lower than those in the vehicle controls (male: vehicle control, 15/50; low dose, 2/50; high dose, 0/50; female: 12/50; 2/50; 2/50). These incidences were believed to be mainly a function of reduced survival.

III. RESULTS: MICE

SINGLE-ADMINISTRATION STUDIES

All mice that received 2,500 or 5,000 mg/kg and 1/5 males that received 1,250 mg/kg died within 3 days after dosing (Table 13). Mice that received 1,250, 2,500, or 5,000 mg/kg exhibited ataxia or lethargy after they were dosed; mice that survived were normal after day 1. Final mean body weights of dosed and vehicle control mice were similar.

SIXTEEN-DAY STUDIES

Sixteen of 18 mice that received 1,000 or 2,000 mg/kg died within 3 days (Table 14). No compound-related histopathologic lesions were observed.

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 15). Mice that received 375 or 750 mg/kg exhibited labored breathing, ataxia, and lethargy for up to 30 minutes after they were dosed. Final mean body weights were not compound related. Liver weight to body weight ratios for dosed mice were not related to the dose administered (Table 16). No compound-related histopathologic lesions were seen. At the end of the studies, pneumonia virus of mice was present in 2/10 vehicle controls and minute virus of mice was present in 1/10 vehicle controls.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF α-METHYLBENZYL 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	20.0 ± 0.9	24.6 ± 0.4	+4.6 ± 1.2	
313	5/5	20.4 ± 0.7	26.2 ± 0.9	+5.8 ± 1.0	106.5
625	5/5	22.4 ± 0.7	26.4 ± 0.4	+4.0 ± 0.4	107.3
1,250	(d) 4/5	22.8 ± 0.8	24.3 ± 1.2	+1.8 ± 0.3	98.8
2,500	(e) 0/5	22.8 ± 0.4	(f)	(f)	(f)
5,000	(g) 0/5	23.2 ± 0.8	(f)	(f)	(f)
FEMALE					
0	5/5	20.4 ± 0.5	21.4 ± 0.2	+1.0 ± 0.7	
313	5/5	18.6 ± 0.4	21.0 ± 0.5	+2.4 ± 0.5	98.1
625	5/5	19.8 ± 0.8	21.6 ± 0.7	+1.8 ± 0.7	100.9
1,250	5/5	18.2 ± 0.7	20.8 ± 0.7	+2.6 ± 0.2	97.2
2,500	(h) 0/5	19.6 ± 0.9	(f)	(f)	(f)
5,000	(g) 0/5	20.4 ± 0.9	(f)	(f)	(f)

(a) Number surviving/number initially in the 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 weight change of the survivors ± standard error of the mean
(d) Day of death: 1
(e) Day of death: 1,1,2,2,2
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: all 1
(h) Day of death: 1,1,1,1,3

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF α-METHYLBENZYL 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	22.0 ± 1.3	28.2 ± 2.2	+6.2 ± 1.5	
125	4/4	23.8 ± 0.9	27.8 ± 0.6	+4.0 ± 0.4	98.6
250	5/5	26.2 ± 0.7	27.6 ± 1.5	+1.4 ± 1.5	97.9
500	5/5	25.6 ± 1.1	29.6 ± 1.5	+4.0 ± 2.0	105.0
1,000	(d) 1/4	21.5 ± 2.1	24.0	−3.0	85.1
2,000	(e) 0/4	18.5 ± 2.2	(f)	(f)	(f)
FEMALE					
0	5/5	16.8 ± 1.0	21.2 ± 0.6	+4.4 ± 0.6	
125	5/5	17.4 ± 1.3	21.6 ± 0.7	+4.2 ± 0.9	101.9
250	5/5	16.8 ± 0.6	22.2 ± 0.8	+5.4 ± 0.9	104.7
500	5/5	20.2 ± 0.4	21.2 ± 0.6	+1.0 ± 0.4	100.0
1,000	(g) 1/5	18.6 ± 0.7	20.0	+3.0	94.3
2,000	(h) 0/5	17.2 ± 0.6	(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: 1,2,3
(e) Day of death: 1,1,2,3
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: all 1
(h) Day of death: 1,1,1,1,2

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF α-METHYLBENZYL 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	23.7 ± 0.4	36.1 ± 0.6	+12.4 ± 0.6	
46.9	9/10	22.7 ± 0.3	36.3 ± 0.6	+13.7 ± 0.7	100.6
93.8	10/10	22.2 ± 0.7	35.1 ± 0.9	+12.9 ± 0.9	97.2
187.5	10/10	24.0 ± 0.5	38.5 ± 1.1	+14.5 ± 0.9	106.6
375	10/10	24.7 ± 0.6	38.5 ± 0.9	+13.8 ± 0.6	106.6
750	10/10	24.8 ± 0.3	36.5 ± 0.5	+11.7 ± 0.7	101.1
FEMALE					
0	10/10	19.5 ± 0.3	27.5 ± 0.9	+8.0 ± 0.7	
46.9	8/10	18.6 ± 0.3	26.3 ± 0.4	+7.4 ± 0.5	95.6
93.8	10/10	18.8 ± 0.3	26.0 ± 0.3	+7.2 ± 0.4	94.5
187.5	10/10	18.5 ± 0.3	26.3 ± 0.4	+7.8 ± 0.4	95.6
375	9/10	17.6 ± 0.3	25.3 ± 0.6	+7.8 ± 0.5	92.0
750	9/10	17.4 ± 0.4	25.8 ± 0.5	+8.4 ± 0.2	93.8

(a) Number surviving/number initially in group; all deaths related to gavage procedure.
(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

TABLE 16. LIVER WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL (a)

Dose (mg/kg)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	35.8 ± 0.72	2,020 ± 56	56.5 ± 1.63
46.9	9	32.8 ± 1.26	1,751 ± 96	53.3 ± 1.64
93.8	10	32.5 ± 1.60	1,788 ± 166	54.2 ± 2.93
187.5	10	38.9 ± 1.07	**2,509 ± 93	*64.5 ± 1.74
375	10	39.0 ± 0.82	2,236 ± 119	57.4 ± 2.89
750	10	36.4 ± 0.52	2,076 ± 63	57.0 ± 1.31
FEMALE				
0	10	26.9 ± 0.70	1,372 ± 61	51.0 ± 1.73
46.9	8	26.2 ± 0.56	1,516 ± 72	58.0 ± 3.31
93.3	10	25.2 ± 0.51	1,353 ± 42	53.9 ± 1.70
187.5	10	26.9 ± 0.47	**1,630 ± 59	**60.6 ± 1.67
375	9	25.5 ± 0.71	1,514 ± 55	*59.5 ± 1.38
750	9	25.5 ± 0.72	1,349 ± 35	53.1 ± 1.66

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
*P<0.05
**P<0.01

Dose Selection Rationale: Because there were deaths at 1,000 mg/kg in the 16-day studies but no deaths or histopathologic lesions attributed to α-methylbenzyl alcohol at 375 or 750 mg/kg in the 13-week studies, these doses were selected for mice for the 2-year studies, administered 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 6%-13% lower than those of vehicle controls from week 10 to week 72 (Table 17 and Figure 10). Mean body weights of high dose female mice were 8%-16% lower than those of vehicle controls from week 72 to the end of the study. Mean body weights of low dose and vehicle control mice were similar. Variable numbers of male and female mice were lethargic or immobile for 1-1.5 hours after they were dosed.

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	375 mg/kg Av. Wt. (grams)	375 mg/kg Wt. (percent of veh. controls)	375 mg/kg No. of Survivors	750 mg/kg Av. Wt. (grams)	750 mg/kg Wt. (percent of veh. controls)	750 mg/kg No. of Survivors
MALE								
0	25.9	50	26.3	102	50	25.8	100	50
1	27.0	49	27.6	102	50	27.4	101	49
2	28.1	49	28.6	102	50	27.7	99	49
3	29.4	49	30.0	102	50	29.1	99	49
4	30.6	48	30.5	100	50	29.7	97	48
5	32.2	48	31.6	98	50	31.1	97	48
6	33.2	48	32.3	97	50	32.1	97	48
7	33.7	48	33.3	99	50	31.7	94	48
8	34.8	48	34.2	98	50	32.7	94	48
9	34.7	48	33.8	97	50	33.4	96	48
10	35.8	48	34.9	97	50	33.0	92	48
11	35.7	48	35.1	98	50	33.5	94	48
12	36.6	48	35.7	98	50	33.4	91	47
14	37.8	48	36.9	98	50	34.4	91	47
16	39.3	48	38.5	98	50	35.8	91	46
20	42.4	48	40.9	96	50	37.7	89	46
24	44.0	48	42.8	97	50	38.3	87	46
28	44.0	47	42.7	97	50	39.2	89	46
32	44.4	47	43.6	98	49	40.2	91	46
36	44.8	47	44.1	98	49	40.6	91	46
40	44.8	47	43.8	98	49	40.0	89	45
44	46.0	47	45.2	98	49	41.1	89	45
48	46.6	47	45.8	98	49	42.6	91	44
52	47.7	47	46.3	97	48	43.5	91	41
56	47.5	47	47.0	99	48	43.1	91	39
60	49.0	47	48.5	99	48	45.4	93	39
64	49.9	47	49.8	100	48	46.6	93	39
68	50.5	46	47.9	95	48	46.3	92	38
72	49.6	46	49.0	99	48	46.0	93	38
76	48.4	45	48.9	101	48	46.4	96	38
80	48.4	45	48.6	100	48	45.4	94	38
84	46.8	45	49.0	105	47	46.3	99	36
88	47.7	44	48.2	101	47	45.8	96	35
93	47.1	43	47.6	101	46	44.5	94	33
96	45.2	42	45.2	100	46	43.1	95	32
100	44.7	40	40.0	89	43	41.8	94	31
FEMALE								
0	19.9	50	19.9	100	50	19.9	100	50
1	20.3	50	20.3	100	50	20.8	102	50
2	21.2	50	21.3	100	50	21.6	102	48
3	22.4	50	22.2	99	50	22.3	100	48
4	22.5	50	22.5	100	50	23.1	103	48
5	23.1	50	23.1	100	50	23.1	100	48
6	23.3	50	23.4	100	50	23.9	103	48
7	24.6	50	24.2	98	50	24.1	98	47
8	26.0	50	26.1	100	50	25.2	97	47
9	26.4	50	25.9	98	50	25.9	98	47
10	26.2	50	26.0	99	50	25.6	98	47
11	26.3	50	26.1	99	50	26.4	100	47
12	26.3	50	25.9	98	50	25.8	98	47
14	26.0	50	26.5	102	50	27.0	104	47
16	27.8	50	28.1	101	50	28.3	102	46
21	29.1	50	30.3	104	50	30.0	103	46
24	30.5	50	30.8	101	50	30.0	98	46
28	30.9	50	31.9	103	49	30.9	100	46
32	32.0	50	32.2	101	49	31.5	98	46
36	31.4	50	31.9	102	49	31.6	101	46
40	32.0	50	32.4	101	49	31.8	99	46
44	33.3	49	33.4	100	49	32.6	98	46
48	33.7	49	34.0	101	49	33.5	99	46
52	33.7	49	34.1	101	49	33.5	99	46
56	36.0	49	36.1	100	49	35.4	98	46
60	38.0	49	38.3	101	49	37.3	98	46
64	40.0	49	40.2	101	49	37.8	95	46
68	40.8	49	41.1	101	49	37.9	93	45
72	42.1	48	41.8	99	48	37.4	89	45
76	43.4	48	42.6	98	48	39.3	91	44
80	43.4	48	43.8	101	48	39.9	92	40
84	43.2	48	43.6	101	48	39.4	91	40
88	44.3	46	44.1	100	47	40.3	91	38
93	44.5	46	43.5	98	45	39.9	90	38
96	42.8	46	42.5	99	44	35.8	84	38
100	43.8	44	42.3	97	43	37.6	86	38

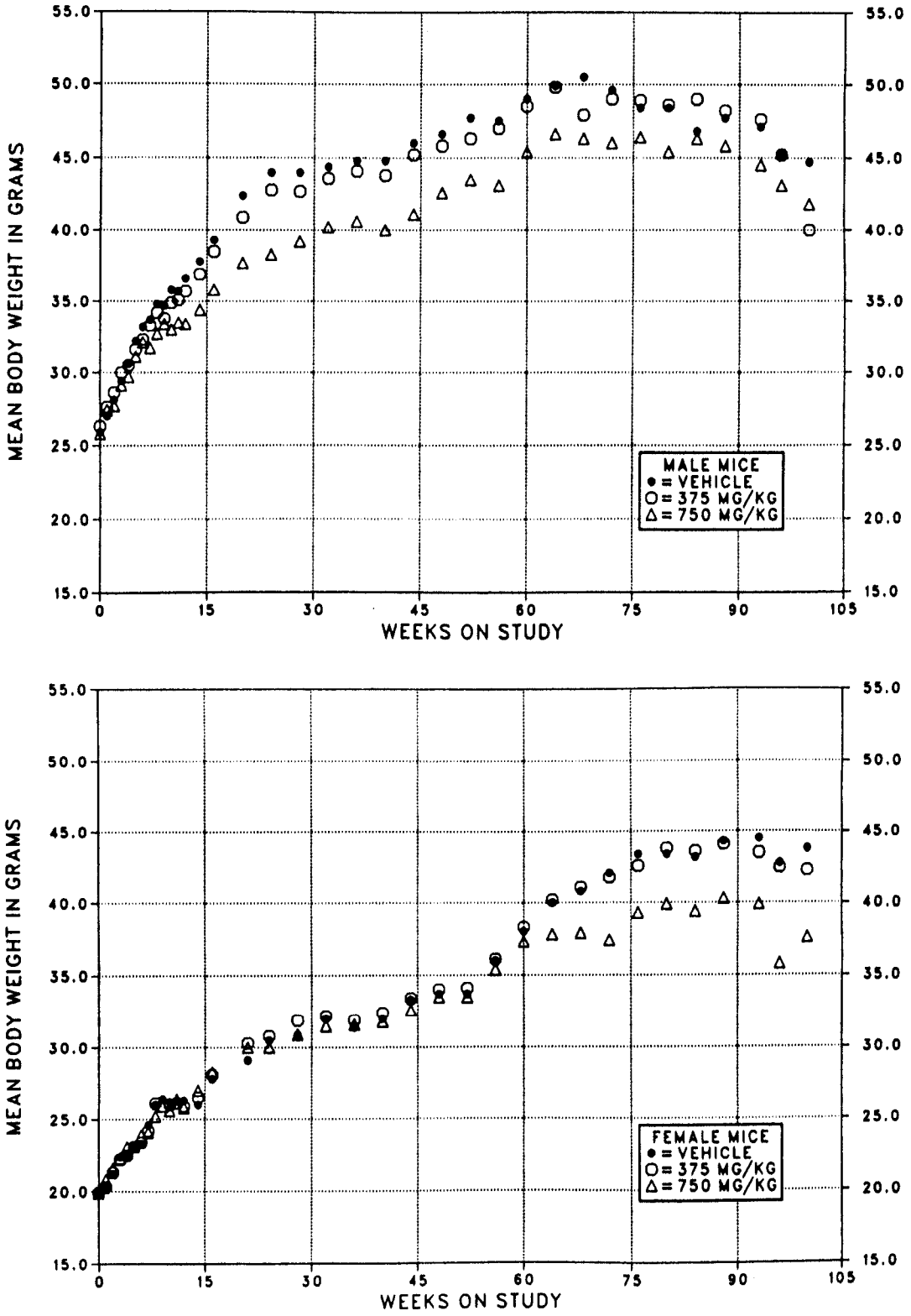

FIGURE 10. GROWTH CURVES FOR MICE EXPOSED TO α-METHYLBENZYL ALCOHOL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered α-methylbenzyl alcohol at the doses used in these studies and for vehicle controls are shownin Table 18 and in the Kaplan and Meier curves in Figure 11. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with nonneoplastic lesions of the lung and neoplastic lesions of the circulatory system.

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 18. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

	Vehicle Control	375 mg/kg	750 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	8	9	14
Moribund kills	0	0	0
Killed accidentally	2	1	8
Animals missexed	1	0	0
Animals surviving until study termination	39	40	28
Survival P values (b)	0.082	0.905	0.118
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	(c) 9	(c) 9	7
Moribund kills	1	0	0
Killed accidentally	0	1	5
Animals surviving until study termination	41	41	38
Survival P values (b)	0.898	0.812	0.989

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(c) One animal died during the termination period and was combined, for statistical purposes, with those killed at termination.

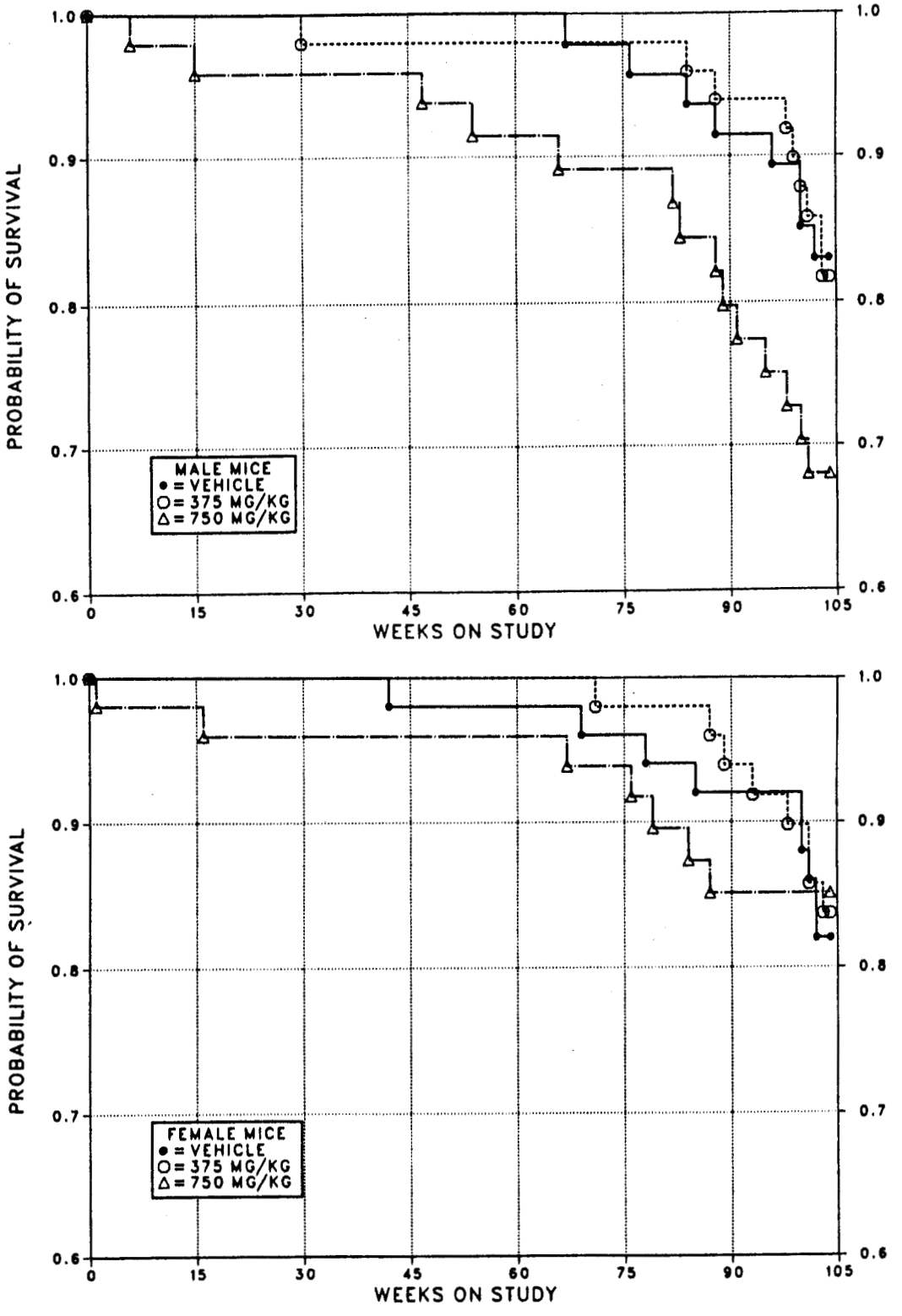

FIGURE 11. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO α-METHYLBENZYL ALCOHOL BY GAVAGE FOR TWO YEARS

Lung: Congestion was observed in seven high dose male and seven high dose female mice (none were observed in the other groups). Hemorrhage and foreign material were observed at increased incidences in high dose male mice (hemorrhage--male: 1/49; 1/50; 6/50; female: 3/50; 1/4; 7/50; foreign material--male: 1/49; 0/50; 7/50; $P < 0.05$; female: 0/50; 0/4; 1/50).

Circulatory System: Hemangiosarcomas and hemangiomas or hemangiosarcomas (combined) in male mice occurred with significant negative trends; the incidences in the high dose group were significantly lower than those in the vehicle controls (Table 19). The slight decrease in vascular tumors is not believed to be related to the administration of α-methylbenzyl alcohol.

TABLE 19. CIRCULATORY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL (a)

	Vehicle Control	375 mg/kg	750 mg/kg
Hemangioma			
Overall Rates	1/49 (2%)	1/49 (2%)	0/50 (0%)
Hemangiosarcoma			
Overall Rates	5/49 (10%)	4/50 (8%)	0/50 (0%)
Terminal Rates	3/39 (8%)	4/40 (10%)	0/28 (0%)
Week of First Observation	76	104	
Incidental Tumor Tests	P=0.044N	P=0.603N	P=0.040N
Hemangioma or Hemangiosarcoma (b)			
Overall Rates	6/49 (12%)	5/50 (10%)	0/50 (0%)
Terminal Rates	4/39 (10%)	5/40 (13%)	0/28 (0%)
Week of First Observation	76	104	
Incidental Tumor Tests	P=0.030N	P=0.590N	P=0.025N

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean ± SD): 11/148 (7% ± 5%); historical incidence in NTP studies: 124/2,091 (6% ± 5%)

α-Methylbenzyl alcohol was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in the presence or absence of exogenous metabolic activation. α-Methylbenzyl alcohol produced a positive response without activation in the mouse L5178Y/TK$^{+/-}$ lymphoma assay for induction of trifluorothymidine resistance; it was not tested with activation. In cytogenetic tests with Chinese hamster ovary (CHO) cells, α-methylbenzyl alcohol induced chromosomal aberrations in the presence, but not the absence, of metabolic activation; no induction of sister chromatid exchanges was observed in CHO cells after exposure to α-methylbenzyl alcohol in either the presence or absence of metabolic activation. The methodology and full results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

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Repeated administration of α-methylbenzyl alcohol at doses of 1,000 mg/kg or higher was lethal to rats and mice in 2-week and 13-week studies; however, the toxic responses observed in the surviving animals were unremarkable, except for the clinical signs of ataxia, hyperpnea, and lethargy, which lasted for about 30 minutes after dosing. The only histopathologic lesions occurred in the spleen of male rats given 750 mg/kg α-methylbenzyl alcohol, where brown pigment observed in splenic macrophages was considered to represent hemosiderin. There was no indication that renal toxicity might lead to mortality in the 2-year studies, nor were there indications of renal toxicity in the short-term or 2-year benzyl alcohol studies (NTP, 1989). Increases in relative liver weights were observed in the 13-week studies in all dosed groups of female rats and in the male rats administered 375 mg/kg or higher, but the major responses were confined to dose groups above 375 mg/kg. Doses used for the 2-year studies were 375 and 750 mg/kg for both rats and mice, since in the short-term studies there were no deaths or effects on body weight gain at these doses and because the splenic lesions observed in the rats were not considered to be life threatening.

The excessive mortality in the 2-year study in male rats reduced the sensitivity of this study for the detection of a carcinogenic response. Nonetheless, dose-related increases of renal tubular cell adenomas were observed in male rats. The original evaluation of the kidney by standard procedures (microscopic examination of single sections of the left and right kidney) identified small numbers of tubular cell neoplasms in dosed male rats but not in vehicle controls (adenomas or adenocarcinomas, combined: vehicle control, 0/50; low dose, 2/50; high dose, 5/50). Kurokawa et al. (1983) compared results of examination of single vs. multiple sections of kidney and found that incidences were greater with multiple sections. Therefore, the National Toxicology Program (NTP) prepared step-sections of the remaining right and left halves of the kidney to clarify the potential relationship of the tubular cell neoplasms to the administration of α-methylbenzyl alcohol. The step-section review identified 1 additional adenoma in the vehicle control group, 12 in the low dose group, and 9 in the high dose group, with total numbers of adenomas and adenocarcinomas (combined) of 1, 13, and 14 in the vehicle control, low, and high dose groups, respectively. These data clearly demonstrated significantly increased incidences ($P<0.001$) of renal tubular cell adenomas in male rats given α-methylbenzyl alcohol.

These renal neoplasm incidences were among the greatest ever recorded in the NTP data base, prompting the Program to consider both "some" and "clear" levels of evidence for carcinogenic activity. Some of the arguments that can be made to support a conclusion of clear level of evidence follow. Since all of these neoplasms were found in rats that died between weeks 81 and 104 of the study, an even greater number of renal neoplasms might have occurred had a larger number of animals been at risk for development of the late-appearing neoplasms. Tubular cell neoplasms have occurred rarely, suggesting that they may be chemically related. The marked increase of benign neoplasms is one of the criteria in the definition of clear evidence. However, it was concluded that the data better represented "some evidence of carcinogenic activity," rather than "clear evidence," for the following reasons: standard histologic procedures (single sections of kidney) showed only small numbers of tubular cell neoplasms in dosed male rats; the current data base for renal neoplasms identified by step-sections is still limited; the tubular cell neoplasms in dosed rats were all adenomas except for one adenocarcinoma; the adenomas were small, microscopic tumors; some were difficult to distinguish from hyperplasia; and the biologic potential of many of the small adenomas is uncertain.

α-Methylbenzyl alcohol was toxic to the kidney, causing an exacerbation of the spontaneous, age-related nephropathy. The tubular cell adenomas occurred only in rats with advanced (moderate or marked severity) renal disease. An increased rate of cell replication occurs as a repair mechanism after toxic injury in many tissues, and this response was reported for the renal tubular epithelium (Charbonneau et al., 1987; Short et al., 1987). Whether such an increase in cell replication contributed to the development of renal neoplasms in this study is unknown.

There was no indication that the renal toxicity was connected with male F344 rat $\alpha_{2\mu}$-globulin induction (Short et al., 1987), since no compound-related increases in hyaline droplet formation were observed in the short-term studies of α-methylbenzyl alcohol. Under normal circumstances, the protein accumulates in reabsorption droplets (seen as hyaline droplets by light microscopy) in the cytoplasm of tubular epithelial cells, where it causes degeneration and necrosis of the epithelium, granular casts at the junction of the inner and outer stripe of the outer medulla, and tubular epithelial degeneration. This spectrum of changes was not observed in male rats in the 13-week studies of α-methylbenzyl alcohol, suggesting that $\alpha_{2\mu}$-globulin accumulation was not the cause of the kidney toxicity. In the 13-week studies, however, necropsies were performed on rats 3 days after the last dosing. Although the abnormal retention of $\alpha_{2\mu}$-globulin and the apparent increase in hyaline droplets might be expected to diminish over this 3-day postdosing period, other changes, including the granular casts, would not be expected to be resolved within this time frame. Furthermore, there was no indication from the 2-year studies of α-methylbenzyl alcohol that the renal lesions observed represented the consistent pattern of toxicity specific to male rats as was reported in studies of unleaded gasoline (Kitchen, 1984), *d*-limonene (NTP, 1990), 1,4-dichlorobenzene (NTP, 1987a), and dimethyl methylphosphonate (NTP, 1987b).

Several chemicals containing a benzylic acid moiety, including 1′-hydroxysafrole (Drinkwater et al., 1976; Wislocki et al., 1977), chlorobenzilate (NCI, 1978), and a number of hydroxymethyl derivatives of polycyclic aromatic hydrocarbons (Anderson et al., 1985; Hayes et al., 1985), were found to produce various neoplasms in animals. The carcinogenic activity of these chemicals might be related to their potential alkylating ability based on the benzyl carbonium ion. This mechanism of action might be considered for the simpler benzyl alcohols, but none of the chemicals from this class, including benzoin (NCI, 1980), ephedrine sulfate (NTP, 1986), phenylephrine hydrochloride (NTP, 1987c), and benzyl alcohol (NTP, 1989), caused neoplasms in 2-year studies. In addition, it was unlikely that a reactive species was involved after administration of α-methylbenzyl alcohol, since no hyperplasia or neoplasms were observed in the stomach, where the acid environment would be conducive for the formation of benzyl carbonium ions.

By comparison, mice were much more tolerant to benzyl alcohol (NTP, 1989) and α-methylbenzyl alcohol toxicity than were male rats. However, no data suggested that there was a species difference in the metabolism of these two benzyl alcohol compounds which could account for the lower mortality in the studies in mice. Hippuric acid was shown to be the predominant urinary excretory product of benzyl alcohol in both rats and mice (Clapp and Young, 1970; Abdo et al., 1985); α-methylbenzyl alcohol was also metabolized to hippuric acid in rabbits and was excreted into the urine together with methylphenylcarbinyl glucuronide (Opdyke, 1974).

Although there was a greater than 10% reduction in body weight gain in the low dose male and the high dose female groups of mice administered α-methylbenzyl alcohol, there was no effect on survival. In addition, no increases in neoplastic or nonneoplastic lesions in mice were attributable to chemical administration. There was a significant negative trend for hemangiosarcomas in male mice. The incidences recorded were 5/49, 4/50, and 0/50 in the vehicle control, low dose, and high dose groups. The spontaneous occurrence of these neoplasms in corn oil vehicle control $B6C3F_1$ male mice is highly variable in NTP studies (6% ± 5%), so their absence from mice in the high dose group could easily be attributed to biologic variability.

The structural analogs benzyl alcohol (NTP, 1989) and β-phenethyl alcohol demonstrated mutagenic profiles similar to that of α-methylbenzyl alcohol, being negative for gene reversion in bacteria (Ishidate et al., 1984; Zeiger and Pagano, 1984; Mortelmans et al., 1986) and positive for induction of petite colonies in yeast (Wilkie and Maroudas, 1969; Kojima et al., 1976). There was evidence of clastogenic activity for α-methylbenzyl alcohol as well as for the two structural analogs. α-Methylbenzyl alcohol was positive in the mouse lymphoma assay without activation and induced chromosomal aberrations in Chinese hamster ovary (CHO)

cells only in the presence of metabolic activation; sister chromatid exchanges (SCEs) were not observed. Benzyl alcohol (Barthelmess and Elkabarity, 1962) and β-phenethyl alcohol (Bammi and Jura, 1966) were reported to induce chromosomal aberrations in *Allium cepa*, but benzyl alcohol was negative in a later test for induction of chromosomal aberrations in Chinese hamster lung fibroblasts (Ishidate et al., 1984). In NTP cytogenetic tests with CHO cells, benzyl alcohol induced chromosomal aberrations in the presence of S9 and SCEs with and without S9.

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

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of α-methylbenzyl alcohol for male F344/N rats, as shown by increased incidences of renal tubular cell adenomas and adenomas or adenocarcinomas (combined). There was *no evidence of carcinogenic activity* for female F344/N rats administered 375 or 750 mg/kg. Renal toxicity characterized by severe nephropathy and related secondary lesions was observed in the dosed rats, and excessive mortality occurred during the last quarter of the studies. Poor survival reduced the sensitivity of the studies for detecting the presence of a carcinogenic response both in chemically exposed groups of male rats and in the high dose group of female rats. There was *no evidence of carcinogenic activity* of α-methylbenzyl alcohol for male or female B6C3F$_1$ mice administered 375 or 750 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 pages 9, 10, and 12.

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APPENDIX A

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

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma	1 (2%)		
Basal cell tumor		1 (2%)	
Keratoacanthoma	1 (2%)		
Sarcoma, NOS			1 (2%)
Fibrosarcoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	8 (16%)		
Fibrosarcoma		1 (2%)	
Fibrous histiocytoma, malignant		1 (2%)	
Myxoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	
Chordoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
Malignant lymphoma, undifferentiated type			1 (2%)
Leukemia, mononuclear cell	15 (30%)	1 (2%)	
#Spleen	(50)	(50)	(48)
Leukemia, mononuclear cell		1 (2%)	
#Mediastinal lymph node	(48)	(47)	(41)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		1 (2%)	
Neurilemoma, malignant	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)	2 (4%)	
#Pancreas	(48)	(50)	(47)
Acinar cell adenoma	2 (4%)	1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	5 (10%)
Tubular cell adenocarcinoma		1 (2%)	
#Urinary bladder	(48)	(46)	(47)
Transitional cell papilloma			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(49)
Chromophobe adenoma	9 (18%)	9 (18%)	2 (4%)
Chromophobe carcinoma	1 (2%)		
#Adrenal	(50)	(50)	(49)
Cortical adenoma	1 (2%)	1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	16 (32%)	19 (38%)	4 (8%)
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(48)	(48)	(41)
Follicular cell adenoma		2 (4%)	2 (5%)
C-cell adenoma	9 (19%)	1 (2%)	
C-cell carcinoma	1 (2%)		1 (2%)
#Parathyroid	(29)	(37)	(35)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(48)	(50)	(47)
Islet cell adenoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)		1 (2%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS		3 (6%)	
Adenoma, NOS	2 (4%)	1 (2%)	
#Testis	(49)	(47)	(46)
Interstitial cell tumor	46 (94%)	36 (77%)	35 (76%)
Mesothelioma, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Squamous cell carcinoma, invasive	1 (2%)		
*Pelvic bones	(50)	(50)	(50)
Osteosarcoma			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	3 (6%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	12	30	37
Moribund sacrifice	2	3	4
Terminal sacrifice	35	8	1
Dosing accident	1	8	8
Accidentally killed, nda		1	
TUMOR SUMMARY			
Total animals with primary tumors**	49	42	38
Total primary tumors	128	88	58
Total animals with benign tumors	49	41	37
Total benign tumors	101	75	52
Total animals with malignant tumors	21	10	4
Total malignant tumors	24	12	4
Total animals with secondary tumors##	2	2	
Total secondary tumors	3	4	
Total animals with tumors-- uncertain benign or malignant	3	1	2
Total uncertain tumors	3	1	2

* 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 α-METHYLBENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 14	C 48	C 07	C 26	C 27	C 40	C 23	C 06	C 22	C 46	C 02	C 50	C 16	C 13	C 42	C 01	C 03	C 04	C 05	C 08	C 09	C 10	C 11	C 12	C 15
WEEKS ON STUDY	000	082	085	089	089	090	092	094	094	095	099	099	100	102	102	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																			X						
Keratoacanthoma																				X					
Fibrosarcoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																			X						
Fibroma																	X	X					X		X
Myxoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic													X												
Alveolar/bronchiolar carcinoma					X																				
Chordoma, metastatic			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant														X											
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																			X						
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma										X		X			X							X		X	
Chromophobe carcinoma					X																				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma					X				X								X		X	X		X			
Thyroid	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma					X											X							X		
C-cell carcinoma																									
Parathyroid	−	+	+	+	+	−	+	−	+	+	+	−	−	+	−	−	−	+	−	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																						X			
Testis	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X
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
Squamous cell carcinoma													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
Squamous cell carcinoma, invasive													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
Mesothelioma, NOS						X									X		X								
Malignant lymphoma, NOS											X														
Leukemia, mononuclear cell		X		X			X	X	X	X								X				X		X	

+: Tissue examined *microscopically*
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal 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	C17	C18	C19	C20	C21	C24	C25	C28	C29	C30	C31	C32	C33	C34	C35	C36	C37	C38	C39	C41	C43	C44	C45	C47	C49	TOTAL:
WEEKS ON STUDY	104	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
Squamous cell papilloma		X																								1
Squamous cell carcinoma																										1
Keratoacanthoma																										1
Fibrosarcoma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma								X					X					X				X				8
Myxoma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar carcinoma																										1
Chordoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	−	+	−	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X																	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma																		X								2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma												X	X					X	X							9
Chromophobe carcinoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																									X	1
Pheochromocytoma		X		X	X					X			X	X		X		X	X					X	16
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+		+	+	+	+	+	+	48
C-cell adenoma	X		X															X				X	X	X		9
C-cell carcinoma													X													1
Parathyroid	−	+	+	+	+	−	+	−	−	+	−	+	+	−	−	−	+	+	+	−	+	−	+	−	−	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma															X								X			2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Fibroadenoma																										1
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	46
Prostate	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS													X													2
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	N	N	*50
Squamous cell carcinoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										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
Mesothelioma, NOS																										3
Malignant lymphoma, NOS																										1
Leukemia, mononuclear cell									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 α-METHYLBENZYL ALCOHOL: LOW DOSE

ANIMAL NUMBER	C 1 1 0	C 1 1 5	C 1 1 2	C 0 0 9	C 3 3 7	C 4 4 8	C 4 4 5	C 3 3 8	C 2 2 5	C 3 3 2	C 4 4 6	C 4 4 0	C 2 2 6	C 1 1 4	C 1 1 6	C 2 2 1	C 0 0 2	C 2 2 0	C 2 2 9	C 2 2 2	C 4 4 2	C 4 4 7	C 3 3 3	C 0 0 3	C 2 2 7
WEEKS ON STUDY	0 0 7	0 0 7	0 4 6	0 5 0	0 5 0	0 5 0	0 5 3	0 6 8	0 7 9	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 8 5	0 8 5	0 8 6	0 8 7	0 8 7	0 8 9	0 8 9	0 8 9	0 9 1	0 9 2	0 9 2
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																				X					
Fibrous histiocytoma, malignant													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	–	+	–	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, invasive																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma														X											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma											X					X			X					X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma														X	X					X			X		
Pheochromocytoma, malignant												X													
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																									
Parathyroid	–	–	–	+	–	+	+	–	+	+	–	+	+	–	+	+	+	–	+	+	–	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	N	N	+	+	N	+	+	N	+	N	+	+	N	N	N	+	+	N	N	N
Testis	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+
Interstitial cell tumor								X	X		X	X	X	X	X		X	X	X	X	X				X
Mesothelioma, NOS																									
Prostate	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
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
Squamous cell carcinoma			X																						
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive																									
Alveolar/bronchiolar carcinoma, metastatic																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																	X								

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

ANIMAL NUMBER	C 3 9	C 4 4	C 0 6	C 4 3	C 0 7	C 1 9	C 4 9	C 5 0	C 2 4	C 4 1	C 2 3	C 2 8	C 0 5	C 0 1	C 1 7	C 3 1	C 3 6	C 0 4	C 0 8	C 1 1	C 1 3	C 1 8	C 3 0	C 3 4	C 3 5	TOTAL:
WEEKS ON STUDY	0 9 2	0 9 2	0 9 3	0 9 3	0 9 5	0 9 5	0 9 5	0 9 6	0 9 8	0 9 8	0 9 9	0 9 9	1 0 0	1 0 1	1 0 1	1 0 1	1 0 1	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
Basal cell tumor				X																						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																					X		X			2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell		X																								1
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
Alveolar/bronchiolar carcinoma, meta																					X					1
Thymus	+	−	+	+	+	−	−	+	−	−	−	−	+	+	+	−	+	+	+	−	−	+	+	−	−	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, inv																					X					1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X																2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Small intestine	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																							X			1
Tubular cell adenocarcinoma															X											1
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma				X						X		X		X				X								9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma						X																				1
Pheochromocytoma	X			X		X		X			X	X		X	X	X		X	X	X	X			X	X	19
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma			X																						X	2
C-cell adenoma								X																		1
Parathyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	N	N	+	+	+	+	+	+	N	+	N	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	36
Mesothelioma, NOS																								X		1
Prostate	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS		X																	X							3
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	N	N	*50
Squamous cell carcinoma																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, inv																							X			1
Alveolar/bronchiolar carcinoma, meta																					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																										1

* Animals necropsied

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

ANIMAL NUMBER	C042	C002	C038	C045	C046	C007	C005	C044	C029	C049	C023	C025	C013	C050	C016	C001	C010	C037	C048	C040	C047	C021	C018	C024	C026
WEEKS ON STUDY	000	001	002	002	032	039	052	053	061	061	063	065	069	071	072	075	075	075	077	078	078	080	081	081	081
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Transitional cell papilloma																								X	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																				X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																					X				X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	−	+	+
Follicular cell adenoma																									
C-cell carcinoma																						X			
Parathyroid	−	−	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	−	+	+	−	−	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	N	N	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	N	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Interstitial cell tumor									X		X		X	X	X	X		X	X	X	X	X		X	X
Mesothelioma, NOS																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Osteosarcoma														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
Mesothelioma, NOS										X															
Malignant lymphoma, undifferentiated type											X														

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

ANIMAL NUMBER	C30	C35	C36	C06	C39	C43	C14	C33	C41	C20	C08	C28	C32	C04	C19	C17	C15	C03	C31	C09	C12	C22	C34	C27	C11	TOTAL:
WEEKS ON STUDY	082	082	082	083	083	083	084	084	084	086	087	087	087	088	088	089	090	091	091	092	092	092	096	097	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									1
Trachea	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	−	+	+	41
Thymus	−	+	+	+	+	−	−	+	−	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	39
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma						X				X	X												X		X	5
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
Transitional cell papilloma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma								X																		2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma											X														X	4
Thyroid	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	41
Follicular cell adenoma	X																								X	2
C-cell carcinoma																										1
Parathyroid	+	−	+	+	+	+	−	+	+	−	−	−	+	−	−	+	+	+	+	+	+	+	+	+	+	35
Adenoma, NOS																	X									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	*50
Fibroadenoma																							X			1
Testis	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	46
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	35
Mesothelioma, NOS																					X					1
Prostate	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
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
Mesothelioma, NOS																										1
Malignant lymphoma, undiffer type																										1

* Animals necropsied

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

	Vehicle Control	375 mg/kg	750 mg/kg
Integumentary System: Fibroma			
Overall Rates (a)	8/50 (16%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	22.9%	0.0%	0.0%
Terminal Rates (c)	8/35 (23%)	0/8 (0%)	0/1 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.139N	P=0.163N	P=0.748N
Incidental Tumor Tests (d)	P=0.139N	P=0.163N	P=0.748N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.003N	P=0.003N
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	9/50 (18%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	25.7%	3.2%	0.0%
Terminal Rates (c)	9/35 (26%)	0/8 (0%)	0/1 (0%)
Week of First Observation	104	89	
Life Table Tests (d)	P=0.218N	P=0.311N	P=0.718N
Incidental Tumor Tests (d)	P=0.090N	P=0.205N	P=0.718N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.008N	P=0.001N
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	(e) 10/50 (20%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	28.6%	3.2%	5.3%
Terminal Rates (c)	10/35 (29%)	0/8 (0%)	0/1 (0%)
Week of First Observation	104	89	84
Life Table Tests (d)	P=0.482N	P=0.263N	P=0.538
Incidental Tumor Tests (d)	P=0.171N	P=0.169N	P=0.755N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.004N	P=0.004N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (f)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.1%	27.4%	11.1%
Terminal Rates (c)	0/35 (0%)	2/8 (25%)	0/1 (0%)
Week of First Observation	89	89	90
Life Table Tests (d)	P=0.043	P=0.064	P=0.383
Incidental Tumor Tests (d)	P=0.539	P=0.225	P=0.409N
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/50 (30%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	35.3%	6.5%	0.0%
Terminal Rates (c)	9/35 (26%)	0/8 (0%)	0/1 (0%)
Week of First Observation	82	86	
Life Table Tests (d)	P=0.044N	P=0.101N	P=0.263N
Incidental Tumor Tests (d)	P<0.001N	P<0.001N	P=0.003N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
Kidney: Tubular Cell Adenoma			
Overall Rates (f)	0/50 (0%)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	0.0%	12.5%	100.0%
Terminal Rates (c)	0/35 (0%)	1/8 (13%)	1/1 (100%)
Week of First Observation		104	83
Life Table Tests (d)	P<0.001	P=0.210	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.210	P=0.010
Cochran-Armitage Trend Test (d)	P=0.011		
Fisher Exact Test (d)		P=0.500	P=0.028

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

	Vehicle Control	375 mg/kg	750 mg/kg
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (f)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	0.0%	19.8%	100.0%
Terminal Rates (c)	0/35 (0%)	1/8 (13%)	1/1 (100%)
Week of First Observation		101	83
Life Table Tests (d)	P<0.001	P=0.033	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.141	P=0.010
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.247	P=0.028
Anterior Pituitary Gland: Chromophobe Adenoma			
Overall Rates (f)	9/50 (18%)	9/49 (18%)	2/49 (4%)
Adjusted Rates (b)	23.3%	40.4%	8.3%
Terminal Rates (c)	6/35 (17%)	1/8 (13%)	0/1 (0%)
Week of First Observation	95	82	78
Life Table Tests (d)	P=0.041	P=0.024	P=0.257
Incidental Tumor Tests (d)	P=0.165N	P=0.588	P=0.461N
Cochran-Armitage Trend Test (d)	P=0.031N		
Fisher Exact Test (d)		P=0.584	P=0.028N
Anterior Pituitary Gland: Chromophobe Adenoma or Carcinoma			
Overall Rates (f)	10/50 (20%)	9/49 (18%)	2/49 (4%)
Adjusted Rates (b)	24.9%	40.4%	8.3%
Terminal Rates (c)	6/35 (17%)	1/8 (13%)	0/1 (0%)
Week of First Observation	89	82	78
Life Table Tests (d)	P=0.072	P=0.045	P=0.344
Incidental Tumor Tests (d)	P=0.064N	P=0.472N	P=0.160N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.520N	P=0.015N
Adrenal Medulla: Pheochromocytoma			
Overall Rates (f)	16/50 (32%)	19/50 (38%)	4/49 (8%)
Adjusted Rates (b)	42.6%	88.1%	100.0%
Terminal Rates (c)	14/35 (40%)	6/8 (75%)	1/1 (100%)
Week of First Observation	89	85	78
Life Table Tests (d)	P<0.001	P<0.001	P=0.039
Incidental Tumor Tests (d)	P=0.252	P=0.013	P=0.688N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.338	P=0.003N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (f)	16/50 (32%)	20/50 (40%)	4/49 (8%)
Adjusted Rates (b)	42.6%	88.4%	100.0%
Terminal Rates (c)	14/35 (40%)	6/8 (75%)	1/1 (100%)
Week of First Observation	89	83	78
Life Table Tests (d)	P<0.001	P<0.001	P=0.039
Incidental Tumor Tests (d)	P=0.302	P=0.010	P=0.688N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.266	P=0.003N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (f)	9/48 (19%)	1/48 (2%)	0/41 (0%)
Adjusted Rates (b)	25.2%	5.6%	0.0%
Terminal Rates (c)	8/34 (24%)	0/8 (0%)	0/1 (0%)
Week of First Observation	89	96	
Life Table Tests (d)	P=0.190N	P=0.274N	P=0.567N
Incidental Tumor Tests (d)	P=0.052N	P=0.112N	P=0.201N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.008N	P=0.003N

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

	Vehicle Control	375 mg/kg	750 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (f)	10/48 (21%)	1/48 (2%)	1/41 (2%)
Adjusted Rates (b)	28.0%	5.6%	3.4%
Terminal Rates (c)	9/34 (26%)	0/8 (0%)	0/1 (0%)
Week of First Observation	89	96	80
Life Table Tests (d)	P=0.410N	P=0.231N	P=0.657
Incidental Tumor Tests (d)	P=0.119N	P=0.091N	P=0.343N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.004N	P=0.008N
Preputial Gland: Carcinoma			
Overall Rates (f)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	17.9%	0.0%
Terminal Rates (c)	0/35 (0%)	1/8 (13%)	0/1 (0%)
Week of First Observation		83	
Life Table Tests (d)	P=0.181	P=0.031	(g)
Incidental Tumor Tests (d)	P=0.676N	P=0.131	(g)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(g)
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (f)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	5.5%	17.9%	0.0%
Terminal Rates (c)	1/35 (3%)	1/8 (13%)	0/1 (0%)
Week of First Observation	102	83	
Life Table Tests (d)	P=0.331	P=0.122	P=0.974N
Incidental Tumor Tests (d)	P=0.351N	P=0.519	P=0.735N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N
Testis: Interstitial Cell Tumor			
Overall Rates (f)	46/49 (94%)	36/47 (77%)	35/46 (76%)
Adjusted Rates (b)	97.9%	100.0%	100.0%
Terminal Rates (c)	34/35 (97%)	8/8 (100%)	1/1 (100%)
Week of First Observation	82	68	61
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.339	P=0.563N	P=0.782
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.017N	P=0.015N
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	7.6%	12.5%	18.7%
Terminal Rates (c)	1/35 (3%)	1/8 (13%)	0/1 (0%)
Week of First Observation	90	104	61
Life Table Tests (d)	P=0.110	P=0.701	P=0.172
Incidental Tumor Tests (d)	P=0.391N	P=0.367N	P=0.306N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.309N	P=0.500N
All Sites: Benign Tumors			
Overall Rates (a)	49/50 (98%)	41/50 (82%)	37/50 (74%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	35/35 (100%)	8/8 (100%)	1/1 (100%)
Week of First Observation	82	68	61
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.448N	P=0.445N	P=0.591N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.008N	P=0.001N

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

	Vehicle Control	375 mg/kg	750 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	46.0%	51.9%	13.2%
Terminal Rates (c)	11/35 (31%)	3/8 (38%)	0/1 (0%)
Week of First Observation	82	46	63
Life Table Tests (d)	P=0.285	P=0.373	P=0.342
Incidental Tumor Tests (d)	P<0.001N	P=0.013N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.015N	P<0.001N
All Sites: All Tumors			
Overall Rates (a)	49/50 (98%)	42/50 (84%)	38/50 (76%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	35/35 (100%)	8/8 (100%)	1/1 (100%)
Week of First Observation	82	46	61
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.376N	P=0.530N	P=0.591N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.016N	P=0.001N

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) A myxoma was also observed in an animal with a fibroma.
(f) Number of tumor-bearing animals/number of animals examined microscopically at the site
(g) No P value is reported because no tumors were observed in the 750 mg/kg and vehicle control groups.

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

Study	Incidence of Adenomas or Adenocarcinomas in Vehicle Controls
Historical Incidence at Microbiological Associates	
d-Limonene	0/50
Benzyl alcohol	0/48
α-Methylbenzyl alcohol	0/50
TOTAL	0/148 (0.0%)
SD (b)	0.00%
Range (c)	
High	0/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 11/2,092 (0.5%)
SD (b)	0.89%
Range (c)	
High	1/48
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes four tubular cell adenomas, two adenocarcinomas, NOS, and five tubular cell adenocarcinomas

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

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Microbiological Associates	
d-Limonene	(b) 1/48
Benzyl alcohol	0/47
α-Methylbenzyl alcohol	0/48
TOTAL	1/143 (0.7%)
SD (c)	1.20%
Range (d)	
High	1/48
Low	0/48
Overall Historical Incidence	
TOTAL	(e) 5/2,034 (0.2%)
SD (c)	0.80%
Range (d)	
High	2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Papilloma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes three papillomas and two carcinomas

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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)
Edema, NOS		1 (2%)	
Ulcer, NOS	1 (2%)		
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Inflammation, granulomatous		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(47)	(50)	(50)
Foreign body, NOS	1 (2%)	3 (6%)	6 (12%)
Inflammation, suppurative	7 (15%)	24 (48%)	30 (60%)
Inflammation, chronic	1 (2%)		
Infection, fungal	1 (2%)	2 (4%)	1 (2%)
Foreign material, NOS	1 (2%)		4 (8%)
Hyperplasia, NOS	3 (6%)	4 (8%)	2 (4%)
Metaplasia, squamous			2 (4%)
#Nose	(47)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		
*Larynx	(50)	(50)	(50)
Hemorrhage		4 (8%)	
#Trachea	(50)	(50)	(46)
Hemorrhage			1 (2%)
Inflammation, acute necrotizing			1 (2%)
#Lung/bronchus	(50)	(50)	(50)
Infection, fungal			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS	4 (8%)	8 (16%)	10 (20%)
Edema, NOS			3 (6%)
Hemorrhage		1 (2%)	5 (10%)
Pneumonia, aspiration		1 (2%)	1 (2%)
Bronchopneumonia, acute		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
Granuloma, NOS	4 (8%)		1 (2%)
Cholesterol deposit			1 (2%)
Foreign material, NOS		2 (4%)	4 (8%)
Pigmentation, NOS	11 (22%)	9 (18%)	10 (20%)
Hyperplasia, adenomatous	10 (20%)	4 (8%)	1 (2%)
Histiocytosis	9 (18%)	9 (18%)	6 (12%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(48)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, granulocytic		2 (4%)	
#Spleen	(50)	(50)	(48)
Inflammation, acute necrotizing			1 (2%)
Fibrosis	4 (8%)	2 (4%)	
Necrosis, NOS		1 (2%)	
Amyloidosis	1 (2%)		
Metamorphosis, fatty	2 (4%)		
Pigmentation, NOS		1 (2%)	4 (8%)
Atrophy, NOS	2 (4%)	5 (10%)	1 (2%))

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Spleen (Continued)	(50)	(50)	(48)
Plasmacytosis	1 (2%		
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	2 (4%)		
#Splenic follicles	(50)	(50)	(48)
Atrophy, NOS			1 (2%)
#Mandibular lymph node	(48)	(47)	(41)
Hemorrhage			1 (2%)
Inflammation, acute		2 (4%)	1 (2%)
Plasmacytosis		1 (2%)	
#Tracheal lymph node	(48)	(47)	(41)
Inflammation, acute			1 (2%)
#Mediastinal lymph node	(48)	(47)	(41)
Hemorrhage	1 (2%)		
#Mesenteric lymph node	(48)	(47)	(41)
Hemorrhage	1 (2%)		
Inflammation, necrotizing granulomatous		1 (2%)	
Histiocytosis			1 (2%)
#Lung	(50)	(50)	(50)
Erythrophagocytosis			1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis		1 (2%)	
#Thymus	(40)	(33)	(36)
Cyst, NOS		1 (3%)	
Hemorrhage			3 (8%)
Hyperplasia, epithelial		1 (3%)	
CIRCULATORY SYSTEM			
#Brain	(50)	(50)	(49)
Thrombosis, NOS			1 (2%)
#Mandibular lymph node	(48)	(47)	(41)
Lymphangiectasis	1 (2%)	1 (2%)	1 (2%)
#Mediastinal lymph node	(48)	(47)	(41)
Lymphangiectasis	1 (2%)		
#Mesenteric lymph node	(48)	(47)	(41)
Lymphangiectasis	3 (6%)		
#Heart	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	24 (48%)	37 (74%)	15 (30%)
Fibrosis			2 (4%)
Calcification, NOS	1 (2%)	9 (18%)	
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS	3 (6%)	1 (2%)	
*Blood vessel	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
Calcification, NOS		1 (2%)	
*Mediastinal artery	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Hepatic artery	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Splenic artery	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
*Mesenteric artery	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Testis	(49)	(47)	(46)
Perivasculitis	1 (2%)		
#Adrenal medulla	(50)	(50)	(49)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
*Lip	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, pseudoepitheliomatous	1 (2%)		
*Periodontal tissues	(50)	(50)	(50)
Inflammation, acute	1 (2%)		1 (2%)
#Salivary gland	(49)	(43)	(39)
Inflammation, acute	1 (2%)	12 (28%)	9 (23%)
Inflammation, acute/chronic			1 (3%)
Inflammation, chronic		1 (2%)	1 (3%)
Cytomegaly	1 (2%)		
Metaplasia, squamous			1 (3%)
#Liver	(50)	(50)	(50)
Hernia, NOS	3 (6%)	3 (6%)	3 (6%)
Cyst, NOS	1 (2%)		
Congestion, NOS	2 (4%)	2 (4%)	4 (8%)
Inflammation, acute necrotizing		2 (4%)	2 (4%)
Inflammation, chronic suppurative		1 (2%)	
Granuloma, NOS	1 (2%)		
Necrosis, focal	3 (6%)	1 (2%)	2 (4%)
Metamorphosis, fatty	4 (8%)	1 (2%)	
Hemosiderosis	1 (2%)		1 (2%)
Cytologic alteration, NOS	5 (10%)	3 (6%)	1 (2%)
Angiectasis	4 (8%)		1 (2%)
#Hepatic capsule	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Abscess, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
Angiectasis		1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Congestion, NOS		1 (2%)	1 (2%)
Degeneration, NOS	1 (2%)	2 (4%)	2 (4%)
Necrosis, NOS		8 (16%)	7 (14%)
Necrosis, diffuse			1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Atrophy, NOS	1 (2%)		
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	43 (86%)	35 (70%)	29 (58%)
#Pancreas	(48)	(50)	(47)
Dilatation/ducts		1 (2%)	
Hyperplasia, NOS		1 (2%)	1 (2%)
#Pancreatic duct	(48)	(50)	(47)
Metaplasia, squamous	1 (2%)		
#Pancreatic acinus	(48)	(50)	(47)
Degeneration, NOS			1 (2%)
Atrophy, NOS	11 (23%)	5 (10%)	1 (2%)
Hyperplasia, NOS	7 (15%)	3 (6%)	2 (4%)
#Esophagus	(49)	(50)	(45)
Hemorrhage			1 (2%)
Inflammation, acute suppurative			1 (2%)
#Stomach	(49)	(49)	(47)
Inflammation, acute		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Glandular stomach	(49)	(49)	(47)
Ulcer, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous		1 (2%)	
Granuloma, foreign body		1 (2%)	
Erosion		1 (2%)	1 (2%)
Necrosis, NOS	1 (2%)	1 (2%)	
Calcification, NOS	1 (2%)	8 (16%)	3 (6%)
Multinucleated giant cell		2 (4%)	
#Gastric serosa	(49)	(49)	(47)
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Forestomach	(49)	(49)	(47)
Ulcer, NOS	5 (10%)	2 (4%)	7 (15%)
Inflammation, acute	3 (6%)	11 (22%)	6 (13%)
Inflammation, acute/chronic	1 (2%)	3 (6%)	4 (9%)
Inflammation, chronic		2 (4%)	1 (2%)
Hyperplasia, epithelial	5 (10%)	7 (14%)	9 (19%)
Hyperkeratosis			2 (4%)
#Colon	(48)	(44)	(42)
Ulcer, NOS		1 (2%)	
#Colonic mucosa	(48)	(44)	(42)
Dilatation, NOS			1 (2%)
#Colonic serosa	(48)	(44)	(42)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		
*Rectum	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, acute	4 (8%)	3 (6%)	3 (6%)
Inflammation, chronic		3 (6%)	
Nephropathy	41 (82%)	47 (94%)	46 (92%)
Calcification, NOS	1 (2%)		
Hyperplasia, tubular cell		4 (8%)	4 (8%)
#Kidney/capsule	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Kidney/interstitium	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	2 (4%)	1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Pigmentation, NOS	6 (12%)		2 (4%)
#Kidney/pelvis	(50)	(50)	(50)
Hyperplasia, epithelial	3 (6%)	20 (40%)	4 (8%)
#Urinary bladder	(48)	(46)	(47)
Hemorrhage			1 (2%)
Inflammation, acute	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute/chronic	3 (6%)	2 (4%)	
Hyperplasia, epithelial	3 (6%)	4 (9%)	1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(49)
Cyst, NOS	7 (14%)	2 (4%)	2 (4%)
Hemorrhage	1 (2%)		
Hemosiderosis	1 (2%)		
Hyperplasia, chromophobe cell	6 (12%)	3 (6%)	4 (8%)
Angiectasis	3 (6%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Degeneration, lipoid		4 (8%)	
Cytoplasmic vacuolization	4 (8%)		
Hyperplasia, NOS	3 (6%)		
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, NOS	8 (16%)	4 (8%)	5 (10%)
Hyperplasia, focal	1 (2%)		
#Thyroid	(48)	(48)	(41)
Ultimobranchial cyst		2 (4%)	1 (2%)
Hyperplasia, C-cell	8 (17%)	2 (4%)	1 (2%)
Hyperplasia, follicular cell		1 (2%)	
#Thyroid follicle	(48)	(48)	(41)
Cyst, NOS		1 (2%)	
#Parathyroid	(29)	(37)	(35)
Hyperplasia, NOS		23 (62%)	4 (11%)
#Pancreatic islets	(48)	(50)	(47)
Hyperplasia, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	13 (26%)	4 (8%)	1 (2%)
Hyperplasia, NOS	3 (6%)		1 (2%)
*Preputial gland	(50)	(50)	(50)
Cystic ducts		1 (2%)	
Inflammation, acute	2 (4%)	3 (6%)	1 (2%)
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Hyperplasia, NOS	2 (4%)		
#Prostate	(44)	(44)	(46)
Inflammation, suppurative	4 (9%)	5 (11%)	2 (4%)
Inflammation, chronic suppurative	3 (7%)	2 (5%)	2 (4%)
Hyperplasia, NOS	10 (23%)	10 (23%)	9 (20%)
Metaplasia, squamous	2 (5%)	1 (2%)	
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic suppurative		1 (2%)	
Atrophy, NOS		2 (4%)	2 (4%)
#Testis	(49)	(47)	(46)
Infarct, NOS		1 (2%)	
Atrophy, NOS	3 (6%)	6 (13%)	3 (7%)
Atrophy, diffuse			1 (2%)
Hyperplasia, interstitial cell	4 (8%)	4 (9%)	7 (15%)
*Epididymis	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Compression, NOS	1 (2%)	1 (2%)	
Hemorrhage	2 (4%)		1 (2%)
Infarct, acute	1 (2%)		
*Spinal cord	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, acute			2 (4%)
Atrophy, NOS	1 (2%)	3 (6%)	

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

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute	1 (2%)	2 (4%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic			1 (2%)
Cataract	2 (4%)	11 (22%)	2 (4%)
Atrophy, NOS	1 (2%)		
*Eye/sclera	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Eye/iris	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	1 (2%)	1 (2%)	
Atrophy, NOS		2 (4%)	
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute	3 (6%)		
*Zymbal gland	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
*Middle ear	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic suppurative	1 (2%)		
*Internal ear	(50)	(50)	(50)
Metaplasia, squamous	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	21 (42%)	7 (14%)
*Laryngeal muscle	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Muscle hip/thigh	(50)	(50)	(50)
Atrophy, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
*Inguinal region	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
Necrosis, fat	1 (2%)		
*Pleura	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Inflammation, acute suppurative	1 (2%)		1 (2%)
Inflammation, acute/chronic		2 (4%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, necrotizing granulomatous	6 (12%)	2 (4%)	
Necrosis, fat	1 (2%)		
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, granulomatous	1		

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

	Vehicle Control	Low Dose	High Dose
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 α-METHYLBENZYL ALCOHOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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%)	
Fibroma	1 (2%)	1 (2%)	
Myxosarcoma	1 (2%)		
Neurofibroma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(48)
Adenocarcinoma, NOS, metastatic	1 (2%)	2 (4%)	
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	
Embryonal carcinoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	12 (24%)	2 (4%)	2 (4%)
#Mandibular lymph node	(50)	(48)	(47)
Squamous cell carcinoma, invasive	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(49)
Hepatocellular adenoma		1 (2%)	
#Pancreas	(49)	(48)	(45)
Acinar cell adenoma			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
#Urinary bladder	(49)	(47)	(48)
Transitional cell papilloma			2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Chromophobe adenoma	21 (43%)	24 (48%)	7 (14%)
Chromophobe carcinoma	2 (4%)		
#Adrenal	(49)	(47)	(50)
Cortical adenoma			1 (2%)
Cortical carcinoma			1 (2%)
#Adrenal medulla	(49)	(47)	(50)
Pheochromocytoma	4 (8%)	5 (11%)	
Pheochromocytoma, malignant	2 (4%)		
#Thyroid	(47)	(49)	(48)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	1 (2%)	2 (4%)	
C-cell carcinoma	2 (4%)	1 (2%)	1 (2%)
#Pancreatic islets	(49)	(48)	(45)
Islet cell adenoma		1 (2%)	3 (7%)
Islet cell carcinoma	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	2 (4%)	1 (2%)	
Fibroadenoma	21 (42%)	15 (30%)	5 (10%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	3 (6%)	4 (8%)	3 (6%)
*Vagina	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
#Uterus	(50)	(48)	(49)
Leiomyoma		1 (2%)	
Endometrial stromal polyp	9 (18%)	11 (23%)	4 (8%)
#Cervix uteri	(50)	(48)	(49)
Sarcoma, NOS, invasive		1 (2%)	
#Uterus/endometrium	(50)	(48)	(49)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS		2 (4%)	1 (2%)
#Ovary	(49)	(46)	(48)
Granulosa cell tumor	2 (4%)	1 (2%)	
Embryonal carcinoma			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Granular cell tumor, NOS			1 (2%)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Embryonal carcinoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Squamous cell carcinoma, unclear primary/metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	13	21	24
Moribund sacrifice	2		1
Terminal sacrifice	34	25	11
Dosing accident	1	4	14

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	46	40	22
Total primary tumors	89	77	35
Total animals with benign tumors	41	36	19
Total benign tumors	63	66	27
Total animals with malignant tumors	20	9	7
Total malignant tumors	23	10	7
Total animals with secondary tumors##	2	3	1
Total secondary tumors	3	3	2
Total animals with tumors-- uncertain benign or malignant	2	1	1
Total uncertain tumors	2	1	1
Total animals with tumors-- uncertain primary or metastatic	1		
Total uncertain tumors	1		

* 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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 0 2	C 3 3	C 2 1	C 2 4	C 3 9	C 2 0	C 3 0	C 4 3	C 4 8	C 2 2	C 1 3	C 1 5	C 4 0	C 0 1	C 1 1	C 3 8	C 0 3	C 0 4	C 0 5	C 0 6	C 0 7	C 0 8	C 0 9	C 1 0	C 1 2
WEEKS ON STUDY	0 3 4	0 6 7	0 7 5	0 7 7	0 7 9	0 8 0	0 8 9	0 9 1	0 9 1	0 9 5	0 9 7	0 9 7	0 9 8	1 0 3	1 0 3	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
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibroma																									
Myxosarcoma														X											
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic						X																			
Alveolar/bronchiolar adenoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																						X			
Thymus	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma		X	X			X				X	X			X			X	X		X	X				X
Chromophobe carcinoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X		X													
Pheochromocytoma, malignant					X											X									
Thyroid	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	−	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+	−	+	−	+	+	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS						X																			
Fibroadenoma								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																	X					X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp				X																		X	X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor									X																
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
Squamous cell carcinoma, unclear primary or metastatic																						X			
Leukemia, mononuclear cell	X			X								X	X	X	X						X				

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal 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 1 1 4	C 1 1 6	C 1 1 7	C 1 1 8	C 1 1 9	C 2 2 3	C 2 2 5	C 2 2 6	C 2 2 7	C 2 2 8	C 2 2 9	C 3 1	C 3 2	C 3 4	C 3 5	C 3 6	C 3 7	C 4 1	C 4 4 2	C 4 4 4	C 4 4 5	C 4 6	C 4 7	C 4 9	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																								X		1
Myxosarcoma																										1
Neurofibroma																					X					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma				X		X				X				X	X	X			X	X		X	X			21
Chromophobe carcinoma		X						X																		2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma									X										X							4
Pheochromocytoma, malignant																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell carcinoma												X														1
C-cell adenoma																			X							1
C-cell carcinoma																							X		X	2
Parathyroid	+	+	–	+	–	–	–	+	–	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	34
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																X										2
Fibroadenoma				X		X	X	X		X	X	X	X	X	X		X		X						X	21
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																		3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X																								1
Endometrial stromal polyp				X			X				X					X			X		X					9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor																							X			2
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
Squamous cell carcinoma, unclear primary or metastatic																										1
Leukemia, mononuclear cell	X						X		X						X	X										12

• Animals necropsied

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

ANIMAL NUMBER	C 3 0	C 4 5	C 0 7	C 2 4	C 4 9	C 2 5	C 3 3	C 3 7	C 1 9	C 2 9	C 3 4	C 3 2	C 0 6	C 1 7	C 0 4	C 1 1	C 1 3	C 1 6	C 2 6	C 5 0	C 4 2	C 2 1	C 2 2	C 2 7	C 0 1
WEEKS ON STUDY	0 4 9	0 4 9	0 5 0	0 5 2	0 5 2	0 7 0	0 7 5	0 8 3	0 8 5	0 8 5	0 8 6	0 8 8	0 8 9	0 9 0	0 9 1	0 9 4	0 9 9	0 9 9	0 9 9	0 9 9	1 0 0	1 0 1	1 0 1	1 0 3	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																			X						
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma						X	X		X	X	X				X		X	X			X	X	X		
Adrenal	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma													X												
C-cell carcinoma																									
Parathyroid	+	+	–	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Adenocarcinoma, NOS																							X		
Fibroadenoma									X						X	X						X	X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, 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
Sarcoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adenocarcinoma, NOS																			X						
Sarcoma, NOS, invasive																									
Leiomyoma										X															
Endometrial stromal polyp										X		X				X			X			X	X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+
Granulosa cell tumor																									
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
Leukemia, mononuclear cell								X																X	

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

ANIMAL NUMBER	C 0 2	C 0 3	C 0 5	C 0 8	C 0 9	C 1 0	C 1 2	C 1 4	C 1 5	C 1 8	C 2 0	C 2 3	C 2 8	C 3 1	C 3 5	C 3 6	C 3 8	C 3 9	C 4 0	C 4 1	C 4 3	C 4 4	C 4 6	C 4 7	C 4 8	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+		*50
Sarcoma, NOS													X													1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
Adenocarcinoma, NOS, metastatic										X																2
Alveolar/bronchiolar adenoma									X																	1
Alveolar/bronchiolar carcinoma																				X						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymus	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+		43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
Hepatocellular adenoma			X																							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		45
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Chromophobe adenoma	X	X	X	X		X		X	X			X					X			X	X	X		X		24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
Pheochromocytoma		X					X					X							X				X			5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																							X			2
C-cell carcinoma		X																								1
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	–	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Islet cell adenoma																X										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+		*50
Adenocarcinoma, NOS																										1
Fibroadenoma	X	X		X		X		X				X	X					X	X		X					15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															1
Adenoma, NOS	X																					X	X			4
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
Sarcoma, NOS													X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Adenocarcinoma, NOS										X																2
Sarcoma, NOS, invasive													X													1
Leiomyoma																										1
Endometrial stromal polyp		X			X									X				X						X		11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	46
Granulosa cell tumor										X																1
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		*50
Leukemia, mononuclear cell																										2

* Animals necropsied

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

ANIMAL NUMBER	C 0 2	C 1 0	C 3 8	C 1 8	C 2 3	C 0 8	C 2 5	C 0 7	C 1 7	C 2 0	C 4 9	C 0 4	C 3 0	C 4 5	C 3 1	C 4 4	C 3 3	C 4 3	C 0 5	C 3 2	C 3 7	C 2 6	C 0 6	C 0 1	C 1 3
WEEKS ON STUDY	0 0 0	0 0 0	0 0 0	0 0 1	0 0 3	0 3 7	0 3 8	0 4 0	0 4 4	0 4 6	0 4 8	0 4 9	0 4 9	0 5 0	0 5 2	0 5 2	0 5 3	0 5 3	0 6 2	0 6 3	0 6 4	0 6 7	0 7 7	0 8 1	0 8 3
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+
Embryonal carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	−	−	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																		X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+
C-cell carcinoma																									
Parathyroid	+	+	−	−	−	+	+	+	+	+	−	+	−	−	+	−	−	+	−	+	−	−	+	+	+
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroadenoma																									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	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp												X								X					
Ovary	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Embryonal carcinoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Astrocytoma																									
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																									
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
Embryonal carcinoma, invasive																									
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																									

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

ANIMAL NUMBER	C 1 4	C 4 1	C 3 5	C 2 1	C 1 5	C 4 2	C 2 7	C 1 9	C 3 4	C 4 0	C 2 4	C 0 3	C 1 1	C 1 2	C 0 9	C 1 6	C 2 2	C 2 8	C 2 9	C 3 6	C 3 9	C 4 6	C 4 7	C 4 8	C 5 0	TOTAL:
WEEKS ON STUDY	0 8 4	0 8 4	0 8 6	0 9 1	0 9 2	0 9 2	0 9 3	0 9 6	0 9 6	0 9 6	0 9 8	0 9 9	1 0 1	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	1 0 4	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Embryonal carcinoma, metastatic								X																		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	−	+	−	+	+	+	−	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	−	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Acinar cell adenoma														X												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Small intestine	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	39
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional cell papilloma				X																					X	2
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma					X		X			X										X			X	X		7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																									X	1
Cortical carcinoma																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell carcinoma																							X			1
Parathyroid	−	−	+	+	+	+	+	−	+	+	−	+	−	+	+	−	−	+	+	+	+	+	+	+	+	32
Pancreatic islets	+	+	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Islet cell adenoma											X			X									X			3
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																	X	X					X	X		5
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				X					3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																		X								1
Endometrial stromal polyp																								X	X	4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Embryonal carcinoma								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS														X												1
Astrocytoma					X																					1
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	*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
Embryonal carcinoma, invasive								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				2

* Animals necropsied

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

	Vehicle Control	375 mg/kg	750 mg/kg
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Myxosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.4%	6.7%	0.0%
Terminal Rates (c)	2/34 (6%)	1/26 (4%)	0/11 (0%)
Week of First Observation	103	99	
Life Table Tests (d)	P=0.286N	P=0.607N	P=0.383N
Incidental Tumor Tests (d)	P=0.165N	P=0.528N	P=0.252N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	12/50 (24%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	29.1%	5.9%	18.2%
Terminal Rates (c)	6/34 (18%)	0/26 (0%)	2/11 (18%)
Week of First Observation	34	83	104
Life Table Tests (d)	P=0.042N	P=0.019N	P=0.201N
Incidental Tumor Tests (d)	P=0.002N	P=0.002N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.004N	P=0.004N
Anterior Pituitary Gland: Chromophobe Adenoma			
Overall Rates (e)	21/49 (43%)	24/50 (48%)	7/50 (14%)
Adjusted Rates (b)	51.5%	63.5%	39.8%
Terminal Rates (c)	15/34 (44%)	13/26 (50%)	3/11 (27%)
Week of First Observation	67	70	53
Life Table Tests (d)	P=0.478	P=0.112	P=0.461N
Incidental Tumor Tests (d)	P=0.053N	P=0.215	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.378	P=0.002N
Anterior Pituitary Gland: Chromophobe Adenoma or Carcinoma			
Overall Rates (e)	23/49 (47%)	24/50 (48%)	7/50 (14%)
Adjusted Rates (b)	56.6%	63.5%	39.8%
Terminal Rates (c)	17/34 (50%)	13/26 (50%)	3/11 (27%)
Week of First Observation	67	70	53
Life Table Tests (d)	P=0.492N	P=0.182	P=0.369N
Incidental Tumor Tests (d)	P=0.027N	P=0.335	P=0.035N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.538	P<0.001N
Adrenal Medulla: Pheochromocytoma			
Overall Rates (e)	4/49 (8%)	5/47 (11%)	0/50 (0%)
Adjusted Rates (b)	10.5%	20.0%	0.0%
Terminal Rates (c)	2/34 (6%)	5/25 (20%)	0/11 (0%)
Week of First Observation	95	104	
Life Table Tests (d)	P=0.376N	P=0.331	P=0.259N
Incidental Tumor Tests (d)	P=0.260N	P=0.391	P=0.105N
Cochran-Armitage Trend Test (d)	P=0.068N		
Fisher Exact Test (d)		P=0.473	P=0.056N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (e)	6/49 (12%)	5/47 (11%)	0/50 (0%)
Adjusted Rates (b)	14.9%	20.0%	0.0%
Terminal Rates (c)	2/34 (6%)	5/25 (20%)	0/11 (0%)
Week of First Observation	79	104	
Life Table Tests (d)	P=0.181N	P=0.573	P=0.141N
Incidental Tumor Tests (d)	P=0.065N	P=0.553N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.530N	P=0.012N

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

	Vehicle Control	375 mg/kg	750 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (e)	3/47 (6%)	3/49 (6%)	1/48 (2%)
Adjusted Rates (b)	9.1%	10.1%	9.1%
Terminal Rates (c)	3/33 (9%)	2/26 (8%)	1/11 (9%)
Week of First Observation	104	89	104
Life Table Tests (d)	P=0.585	P=0.556	P=0.725
Incidental Tumor Tests (d)	P=0.550N	P=0.596	P=0.725
Cochran-Armitage Trend Test (d)	P=0.230N		
Fisher Exact Test (d)		P=0.641N	P=0.301N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (e)	0/49 (0%)	1/48 (2%)	3/45 (7%)
Adjusted Rates (b)	0.0%	4.0%	22.2%
Terminal Rates (c)	0/34 (0%)	1/25 (4%)	1/11 (9%)
Week of First Observation		104	98
Life Table Tests (d)	P=0.005	P=0.439	P=0.011
Incidental Tumor Tests (d)	P=0.016	P=0.439	P=0.058
Cochran-Armitage Trend Test (d)	P=0.052		
Fisher Exact Test (d)		P=0.495	P=0.106
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (e)	1/49 (2%)	1/48 (2%)	3/45 (7%)
Adjusted Rates (b)	2.9%	4.0%	22.2%
Terminal Rates (c)	1/34 (3%)	1/25 (4%)	1/11 (9%)
Week of First Observation	104	104	98
Life Table Tests (d)	P=0.029	P=0.692	P=0.043
Incidental Tumor Tests (d)	P=0.065	P=0.692	P=0.131
Cochran-Armitage Trend Test (d)	P=0.179		
Fisher Exact Test (d)		P=0.747	P=0.277
Mammary Gland: Fibroadenoma			
Overall Rates (a)	21/50 (42%)	15/50 (30%)	5/50 (10%)
Adjusted Rates (b)	56.5%	47.2%	38.8%
Terminal Rates (c)	18/34 (53%)	10/26 (38%)	4/11 (36%)
Week of First Observation	91	85	83
Life Table Tests (d)	P=0.223N	P=0.456N	P=0.261N
Incidental Tumor Tests (d)	P=0.057N	P=0.286N	P=0.105N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.149N	P<0.001N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	23/50 (46%)	15/50 (30%)	5/50 (10%)
Adjusted Rates (b)	60.1%	47.2%	38.8%
Terminal Rates (c)	19/34 (56%)	10/26 (38%)	4/11 (36%)
Week of First Observation	80	85	83
Life Table Tests (d)	P=0.128N	P=0.313N	P=0.168N
Incidental Tumor Tests (d)	P=0.021N	P=0.156N	P=0.044N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.074N	P<0.001N
Clitoral Gland: Adenoma			
Overall Rates (e)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	8.8%	14.1%	22.1%
Terminal Rates (c)	3/34 (9%)	3/26 (12%)	2/11 (18%)
Week of First Observation	104	99	92
Life Table Tests (d)	P=0.124	P=0.370	P=0.181
Incidental Tumor Tests (d)	P=0.198	P=0.395	P=0.262
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.500	P=0.661

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

	Vehicle Control	375 mg/kg	750 mg/kg
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (e)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	8.8%	17.9%	22.1%
Terminal Rates (c)	3/34 (9%)	4/26 (15%)	2/11 (18%)
Week of First Observation	104	99	92
Life Table Tests (d)	P=0.105	P=0.230	P=0.181
Incidental Tumor Tests (d)	P=0.169	P=0.250	P=0.262
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Test (d)		P=0.357	P=0.661
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	11/48 (22%)	4/50 (8%)
Adjusted Rates (b)	25.2%	32.4%	22.9%
Terminal Rates (c)	8/34 (24%)	5/26 (19%)	2/11 (18%)
Week of First Observation	77	85	49
Life Table Tests (d)	P=0.356	P=0.219	P=0.540
Incidental Tumor Tests (d)	P=0.334N	P=0.311	P=0.418N
Cochran-Armitage Trend Test (d)	P=0.110N		
Fisher Exact Test (d)		P=0.402	P=0.117N
All Sites: Benign Tumors			
Overall Rates (a)	41/50 (82%)	36/50 (72%)	19/50 (38%)
Adjusted Rates (b)	91.0%	87.5%	79.8%
Terminal Rates (c)	30/34 (88%)	21/26 (81%)	7/11 (64%)
Week of First Observation	67	70	49
Life Table Tests (d)	P=0.180	P=0.325	P=0.221
Incidental Tumor Tests (d)	P=0.015N	P=0.536N	P=0.028N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.172N	P<0.001N
All Sites: Malignant Tumors			
Overall Rates (a)	20/50 (40%)	9/50 (18%)	7/50 (14%)
Adjusted Rates (b)	45.9%	28.8%	50.9%
Terminal Rates (c)	11/34 (32%)	5/26 (19%)	5/11 (45%)
Week of First Observation	34	83	92
Life Table Tests (d)	P=0.304N	P=0.083N	P=0.520N
Incidental Tumor Tests (d)	P=0.023N	P=0.012N	P=0.055N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.014N	P=0.003N
All Sites: All Tumors			
Overall Rates (a)	46/50 (92%)	40/50 (80%)	22/50 (44%)
Adjusted Rates (b)	93.9%	92.9%	90.5%
Terminal Rates (c)	31/34 (91%)	23/26 (88%)	9/11 (82%)
Week of First Observation	34	70	49
Life Table Tests (d)	P=0.138	P=0.343	P=0.174
Incidental Tumor Tests (d)	P=0.002N	P=0.262N	P=0.003N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.074N	P<0.001N

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

TABLE B4a. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas in Vehicle Controls
Historical Incidence at Microbiological Associates	
d-Limonene	0/50
Benzyl alcohol	0/46
α-Methylbenzyl alcohol	0/49
TOTAL	0/145 (0.0%)
SD (b)	0.00%
Range (c)	
High	0/50
Low	0/50
Overall Historical Incidence	
TOTAL	(d) 4/2,026 (0.2%)
SD (b)	0.63%
Range (c)	
High	1/45
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papilloma, NOS; no malignant tumors have been observed.

TABLE B4b. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Microbiological Associates	
d-Limonene	10/50
Benzyl alcohol	8/50
α-Methylbenzyl alcohol	12/50
TOTAL	30/150 (20.0%)
SD (b)	4.00%
Range (c)	
High	12/50
Low	8/50
Overall Historical Incidence	
TOTAL	403/2,100 (19.2%)
SD (b)	7.95%
Range (c)	
High	21/50
Low	2/50

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

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, necrotizing granulomatous	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(48)	(49)
Inflammation, suppurative	3 (6%)	2 (4%)	4 (8%)
Inflammation, acute		1 (2%)	
Foreign material, NOS			1 (2%)
Metaplasia, squamous			1 (2%)
*Larynx	(50)	(50)	(50)
Hemorrhage		2 (4%)	1 (2%)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
#Trachea	(50)	(50)	(47)
Inflammation, acute/chronic			1 (2%)
Inflammation, necrotizing granulomatous	1 (2%)		
#Lung/bronchus	(50)	(49)	(48)
Inflammation, acute			1 (2%)
Inflammation, necrotizing granulomatous	1 (2%)		
#Lung/bronchiole	(50)	(49)	(48)
Inflammation, acute			1 (2%)
#Lung	(50)	(49)	(48)
Congestion, NOS	5 (10%)	17 (35%)	23 (48%)
Edema, NOS	1 (2%)		3 (6%)
Hemorrhage			6 (13%)
Pneumonia, aspiration	1 (2%)		
Bronchopneumonia, acute	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)
Pneumonia, interstitial chronic		1 (2%)	1 (2%)
Granuloma, NOS	11 (22%)	1 (2%)	
Cholesterol deposit		1 (2%)	
Foreign material, NOS		2 (4%)	8 (17%)
Pigmentation, NOS	29 (58%)	39 (80%)	27 (56%)
Hyperplasia, adenomatous	9 (18%)	3 (6%)	1 (2%)
Histiocytosis	30 (60%)	34 (69%)	26 (54%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(48)
Granuloma, NOS	5 (10%)		2 (4%)
Atrophy, NOS			1 (2%)
Hyperplasia, granulocytic		3 (6%)	
#Spleen	(50)	(49)	(46)
Fibrosis	1 (2%)		
Infarct, NOS	1 (2%)		
Pigmentation, NOS	50 (100%)	49 (100%)	44 (96%)
Hematopoiesis	4 (8%)	3 (6%)	1 (2%)
#Mandibular lymph node	(50)	(48)	(47)
Inflammation, acute			1 (2%)
#Pancreatic lymph node	(50)	(48)	(47)
Hemosiderosis		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(50)	(48)	(47)
Inflammation, acute necrotizing		1 (2%)	
Inflammation, granulomatous			1 (2%)
#Liver	(50)	(48)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(45)	(43)	(39)
Ectopia		1 (2%)	
Cyst, NOS		2 (5%)	
Congestion, NOS			2 (5%)
Hemorrhage			2 (5%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Mandibular lymph node	(50)	(48)	(47)
Lymphangiectasis		3 (6%)	1 (2%)
#Heart	(50)	(49)	(49)
Hemorrhage			1 (2%)
Inflammation, chronic	16 (32%)	14 (29%)	13 (27%)
#Heart/atrium	(50)	(49)	(49)
Thrombosis, NOS	1 (2%)	1 (2%)	
*Coronary artery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Liver	(50)	(48)	(49)
Thrombus, organized			1 (2%)
#Ovary	(49)	(46)	(48)
Lymphangiectasis	1 (2%)		
#Adrenal	(49)	(47)	(50)
Thrombus, organized			1 (2%)
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Cyst, NOS			1 (2%)
*Tooth	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Salivary gland	(46)	(49)	(47)
Inflammation, acute		1 (2%)	1 (2%)
#Submaxillary gland	(46)	(49)	(47)
Metaplasia, squamous		1 (2%)	
#Liver	(50)	(48)	(49)
Hernia, NOS	3 (6%)	3 (6%)	2 (4%)
Congestion, NOS	4 (8%)	12 (25%)	4 (8%)
Congestion, chronic passive			1 (2%)
Inflammation, acute necrotizing	1 (2%)	1 (2%)	1 (2%)
Inflammation, active chronic			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic necrotizing		1 (2%)	
Granuloma, NOS	13 (26%)	3 (6%)	2 (4%)
Necrosis, NOS		1 (2%)	
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Metamorphosis, fatty	6 (12%)	1 (2%)	
Cytologic alteration, NOS	13 (26%)	11 (23%)	4 (8%)
Angiectasis	1 (2%)		1 (2%)
#Hepatic capsule	(50)	(48)	(49)
Congestion, NOS	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (*Continued*)			
#Liver/centrilobular	(50)	(48)	(49)
Degeneration, NOS	1 (2%)		
Necrosis, NOS	2 (4%)		
Metamorphosis, fatty	1 (2%)		
Pigmentation, NOS	1 (2%)		
Hypertrophy, NOS			1 (2%)
#Bile duct	(50)	(48)	(49)
Hyperplasia, NOS	23 (46%)	23 (48%)	17 (35%)
#Pancreas	(49)	(48)	(45)
Atrophy, NOS		1 (2%)	
#Pancreatic acinus	(49)	(48)	(45)
Atrophy, NOS	7 (14%)	9 (19%)	5 (11%)
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)
#Pancreas/interstitium	(49)	(48)	(45)
Inflammation, necrotizing granulomatous	1 (2%)		
#Esophagus	(50)	(50)	(46)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
#Glandular stomach	(49)	(48)	(46)
Cyst, NOS		1 (2%)	
Ulcer, NOS			1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, necrotizing granulomatous	1 (2%)		
Erosion	1 (2%)		
Necrosis, NOS	1 (2%)	1 (2%)	
Calcification, NOS	1 (2%)		
#Forestomach	(49)	(48)	(46)
Ulcer, NOS	1 (2%)		1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic	3 (6%)	1 (2%)	
Hyperplasia, epithelial	2 (4%)		1 (2%)
#Duodenum	(49)	(45)	(45)
Inflammation, necrotizing granulomatous	1 (2%)		
#Colonic submucosa	(49)	(44)	(39)
Edema, NOS	2 (4%)		1 (3%)
#Cecum	(49)	(44)	(39)
Inflammation, necrotizing granulomatous	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Mineralization			1 (2%)
Hydronephrosis			1 (2%)
Nephropathy	28 (56%)	39 (80%)	27 (54%)
Pigmentation, NOS			1 (2%)
#Kidney/tubule	(50)	(49)	(50)
Dilatation, NOS	1 (2%)		
Pigmentation, NOS	3 (6%)		1 (2%)
#Kidney/pelvis	(50)	(49)	(50)
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(49)	(47)	(48)
Hyperplasia, epithelial		1 (2%)	
Metaplasia, squamous			1 (2%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(50)
Cyst, NOS	16 (33%)	3 (6%)	4 (8%)
Degeneration, NOS		1 (2%)	
Hemosiderosis			1 (2%)
Hyperplasia, chromophobe cell	1 (2%)	8 (16%)	3 (6%)
Angiectasis	1 (2%)	11 (22%)	3 (6%)
#Adrenal	(49)	(47)	(50)
Degeneration, lipoid		1 (2%)	
#Adrenal cortex	(49)	(47)	(50)
Degeneration, lipoid		5 (11%)	
Cytoplasmic vacuolization	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, NOS	2 (4%)		
#Adrenal medulla	(49)	(47)	(50)
Hyperplasia, NOS	3 (6%)	2 (4%)	
#Thyroid	(47)	(49)	(48)
Ultimobranchial cyst	1 (2%)	2 (4%)	3 (6%)
Inflammation, chronic focal			1 (2%)
Inflammation, necrotizing granulomatous	1 (2%)		
Hyperplasia, C-cell	5 (11%)	7 (14%)	4 (8%)
#Thyroid follicle	(47)	(49)	(48)
Cyst, NOS	1 (2%)		
Hyperplasia, cystic	1 (2%)	2 (4%)	2 (4%)
#Parathyroid	(34)	(38)	(32)
Hyperplasia, NOS	1 (3%)		1 (3%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	22 (44%)	14 (28%)	12 (24%)
Galactocele	1 (2%)		
Abscess, NOS		1 (2%)	
Hyperplasia, NOS	13 (26%)	7 (14%)	3 (6%)
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts	2 (4%)	2 (4%)	
Inflammation, acute		2 (4%)	1 (2%)
Hyperplasia, NOS	1 (2%)		
#Uterus	(50)	(48)	(49)
Hydrometra	1 (2%)	2 (4%)	2 (4%)
Cyst, NOS			1 (2%)
Angiectasis		1 (2%)	
#Cervix uteri	(50)	(48)	(49)
Cyst, NOS	3 (6%)	5 (10%)	3 (6%)
Inflammation, acute	2 (4%)	2 (4%)	4 (8%)
Inflammation, necrotizing granulomatous	1 (2%)		
#Uterus/endometrium	(50)	(48)	(49)
Cyst, NOS	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, cystic	1 (2%)	1 (2%)	2 (4%)
#Endometrial stroma	(50)	(48)	(49)
Hyperplasia, NOS	1 (2%)		
#Ovary/parovarian	(49)	(46)	(48)
Inflammation, necrotizing granulomatous			1 (2%)
#Ovary	(49)	(46)	(48)
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)
Parovarian cyst			1 (2%)
Atrophy, NOS		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Compression, NOS	7 (14%)	2 (4%)	1 (2%)
Hemorrhage		1 (2%)	
Granuloma, NOS	1 (2%)		
*Olfactory sensory epithelium	(50)	(50)	(50)
Inflammation, acute			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		2 (4%)	
Inflammation, acute/chronic		1 (2%)	
Cataract		13 (26%)	4 (8%)
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Atrophy, NOS		2 (4%)	1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, chronic suppurative	1 (2%)		
*Harderian gland	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Laryngeal muscle	(50)	(50)	(50)
Inflammation, acute			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, necrotizing granulomatous	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Pleura	(50)	(50)	(50)
Granuloma, foreign body		1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, necrotizing granulomatous	5 (10%)	8 (16%)	3 (6%)
Necrosis, fat			1 (2%)
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 C

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	1 (2%)	5 (10%)	2 (4%)
Fibrosarcoma	3 (6%)	4 (8%)	2 (4%)
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(50)
Squamous cell carcinoma, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	6 (12%)	4 (8%)	
Alveolar/bronchiolar adenoma	14 (29%)	9 (18%)	8 (16%)
Alveolar/bronchiolar carcinoma	4 (8%)	6 (12%)	1 (2%)
Fibrosarcoma, metastatic	2 (4%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, lymphocytic type		2 (4%)	1 (2%)
Malignant lymphoma, mixed type		4 (8%)	2 (4%)
#Spleen	(48)	(49)	(48)
Malignant lymphoma, mixed type	1 (2%)		
#Mediastinal lymph node	(48)	(50)	(45)
Fibrosarcoma, metastatic	1 (2%)		
#Mesenteric lymph node	(48)	(50)	(45)
Malignant lymphoma, mixed type	1 (2%)		
#Renal lymph node	(48)	(50)	(45)
Squamous cell carcinoma, metastatic		1 (2%)	
#Ileum	(43)	(48)	(40)
Malignant lymphoma, mixed type			1 (3%)
CIRCULATORY SYSTEM			
#Spleen	(48)	(49)	(48)
Hemangioma		1 (2%)	
Hemangiosarcoma		1 (2%)	
#Mesenteric lymph node	(48)	(50)	(45)
Hemangioma	1 (2%)		
#Liver	(49)	(49)	(50)
Hemangiosarcoma	5 (10%)	2 (4%)	
#Testis	(49)	(50)	(49)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(49)	(49)	(50)
Hepatocellular adenoma	13 (27%)	14 (29%)	9 (18%)
Hepatocellular carcinoma	11 (22%)	11 (22%)	5 (10%)
#Forestomach	(46)	(50)	(44)
Squamous cell papilloma	4 (9%)	4 (8%)	2 (5%)
#Duodenum	(43)	(48)	(40)
Adenoma, NOS		1 (2%)	
Adenomatous polyp, NOS	1 (2%)		1 (3%)
#Jejunum	(43)	(48)	(40)
Adenocarcinoma, NOS		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Adrenal	(47)	(46)	(49)
Cortical adenoma			1 (2%)
Pheochromocytoma	1 (2%)	1 (2%)	
Pheochromocytoma, malignant		1 (2%)	1 (2%)
#Adrenal/capsule	(47)	(46)	(49)
Adenoma, NOS	3 (6%)		2 (4%)
#Thyroid	(46)	(49)	(50)
Follicular cell adenoma		1 (2%)	1 (2%)
Follicular cell carcinoma	2 (4%)		
#Pancreatic islets	(46)	(49)	(44)
Islet cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(49)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
#Testis	(49)	(50)	(49)
Interstitial cell tumor	1 (2%)		1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	2 (4%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	9	14
Terminal sacrifice	39	40	28
Dosing accident	2	1	7
Accidentally killed, NOS			1
Animal missexed	1		

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	39	40	32
Total primary tumors	70	71	43
Total animals with benign tumors	28	27	22
Total benign tumors	41	37	29
Total animals with malignant tumors	23	29	13
Total malignant tumors	29	34	14
Total animals with secondary tumors##	8	5	
Total secondary tumors	9	6	

* 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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C014	C024	C040	C050	C042	C006	C033	C045	C012	C039	C011	C001	C002	C003	C004	C005	C007	C008	C009	C010	C013	C015	C016	C017	C018
WEEKS ON STUDY	000	001	025	067	076	084	088	096	100	100	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	S	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Fibroma																									
Fibrosarcoma				X				X			X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X			X	X						X									
Alveolar/bronchiolar adenoma				X									X	X		X		X	X				X	X	
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic				X							X														
Trachea	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	S	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									X
Lymph nodes	S	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic											X														
Hemangioma																								X	
Malignant lymphoma, mixed type												X													
Thymus	S	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+
CIRCULATORY SYSTEM																									
Heart	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	S	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X					X												X
Hepatocellular carcinoma						X		X	X	X						X						X			
Hemangiosarcoma					X						X										X				X
Bile duct	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	S	+	N	+	N	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	S	+	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	S	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	S	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X		X				X							
Small intestine	S	−	−	+	−	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	S	+	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	S	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	S	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Pheochromocytoma																X									
Thyroid	S	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	S	−	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	S	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	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	S	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
Adenoma, NOS																									

+: 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 9	C 2 0	C 2 1	C 2 2	C 2 3	C 2 5	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 1	C 3 2	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 4 1	C 4 3	C 4 4	C 4 6	C 4 7	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*49
Sarcoma, NOS																										1
Fibroma																				X						1
Fibrosarcoma																										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic				X									X													6
Alveolar/bronchiolar adenoma					X				X		X			X	X									X		14
Alveolar/bronchiolar carcinoma		X													X			X							X	4
Fibrosarcoma, metastatic																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic																										1
Hemangioma																										1
Malignant lymphoma, mixed type																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X	X		X		X	X	X		X	X				X									X		13
Hepatocellular carcinoma		X		X					X				X											X		11
Hemangiosarcoma																		X								5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell papilloma																						X				4
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenomatous polyp, NOS			X																							1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS	X																X									3
Pheochromocytoma																										1
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell carcinoma					X																				X	2
Parathyroid	+	–	+	–	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	–	+	37
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	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor															X											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	*49
Carcinoma, NOS																										1
Adenoma, NOS									X													X				2

* Animals necropsied

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

ANIMAL NUMBER	C047	C009	C050	C119	C006	C466	C499	C244	C004	C211	C011	C022	C033	C055	C077	C088	C110	C111	C122	C133	C144	C155	C166	C177	C188
WEEKS ON STUDY	030	049	084	088	098	099	100	101	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X	X							X											
Fibrosarcoma				X		X	X				X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic									X																
Hepatocellular carcinoma, metastatic			X							X					X										
Alveolar/bronchiolar adenoma																	X		X	X	X			X	
Alveolar/bronchiolar carcinoma															X		X						X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X												
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic									X																
Thymus	+	+	−	−	−	−	+	−	−	−	−	+	+	+	−	+	+	+	+	+	+	+	−	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X		X	X		X		X	X			X			
Hepatocellular carcinoma			X				X	X		X				X	X										
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	+	N	+	+	N	N	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma												X								X					
Small intestine	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	−	−	−	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X																			
Pheochromocytoma, malignant					X																				
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																X									
Parathyroid	−	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
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
Squamous cell carcinoma									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																					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					

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

ANIMAL NUMBER	C 2 0	C 2 2	C 2 3	C 2 5	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 1	C 3 2	C 3 3	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 1	C 4 2	C 4 3	C 4 4	C 4 5	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
Fibroma															X	X										5
Fibrosarcoma																										4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic						X																				4
Alveolar/bronchiolar adenoma		X				X												X				X				9
Alveolar/bronchiolar carcinoma							X	X							X											6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Hemangiosarcoma								X																		1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Thymus	+	–	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	–	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X								X	X	X			X				X			X		X			14
Hepatocellular carcinoma						X			X					X				X				X				11
Hemangiosarcoma							X				X															2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	N	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X						X					4
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS									X																	1
Adenocarcinoma, NOS											X															1
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	46
Pheochromocytoma																										1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Parathyroid	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	–	–	–	+	+	–	–	+	+	+	37
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Squamous cell carcinoma																										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																										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										X																2
Malignant lymphoma, mixed type													X							X			X			4

* Animals necropsied

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

ANIMAL NUMBER	C025	C044	C041	C042	C020	C037	C005	C013	C038	C015	C019	C036	C010	C004	C043	C028	C030	C026	C050	C032	C001	C009	C002	C003	C006
WEEKS ON STUDY	000	000	012	015	038	047	050	050	051	054	054	066	082	083	088	089	091	095	098	100	101	102	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																							X	X	
Fibrosarcoma											X										X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X										X							
Alveolar/bronchiolar carcinoma																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	−	−	+	+	+	+	−	+	−	−	+	−	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X			X		
Hepatocellular carcinoma													X	X						X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	N	+	N	N	N	N	+	+	+	N	+	+	N	+	+	+	+	+
Pancreas	+	+	−	+	+	−	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	−	+	−	−	+	+	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Small intestine	+	+	−	+	−	−	−	+	+	+	−	−	−	−	+	+	+	−	+	+	−	+	+	+	+
Adenomatous polyp, NOS																									X
Malignant lymphoma, mixed type																									
Large intestine	+	+	−	+	−	−	−	+	+	+	−	−	−	−	+	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma																									
Pheochromocytoma, malignant																			X						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
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																									
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																									
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						
Malignant lymphoma, lymphocytic type																	X								
Malignant lymphoma, mixed type																X									

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

ANIMAL NUMBER	C 0 7	C 0 8	C 1 1	C 1 2	C 1 4	C 1 6	C 1 7	C 1 8	C 2 1	C 2 2	C 2 3	C 2 4	C 2 7	C 2 9	C 3 1	C 3 3	C 3 4	C 3 5	C 3 9	C 4 0	C 4 5	C 4 6	C 4 7	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
Fibroma																										2
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X								X			X					X		X			8
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X				X	X						X				X	X				X		9
Hepatocellular carcinoma						X					X															5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell papilloma													X													2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenomatous polyp, NOS																										1
Malignant lymphoma, mixed type																	X									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Adenoma, NOS				X																			X			2
Cortical adenoma																						X				1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma										X																1
Parathyroid	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	+	+	−	+	−	+	+	−	−	−	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Islet cell adenoma											X															1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																							X			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
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																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type			X																							2

* Animals necropsied

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

	Vehicle Control	375 mg/kg	750 mg/kg
Integumentary System: Fibroma			
Overall Rates (a)	1/49 (2%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	2.6%	11.6%	7.1%
Terminal Rates (c)	1/39 (3%)	3/40 (7%)	2/28 (7%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.275	P=0.116	P=0.385
Incidental Tumor Tests (d)	P=0.324	P=0.140	P=0.385
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.107	P=0.508
Integumentary System: Fibrosarcoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	6.8%	8.8%	5.7%
Terminal Rates (c)	0/39 (0%)	1/40 (3%)	0/28 (0%)
Week of First Observation	67	88	54
Life Table Tests (d)	P=0.541N	P=0.526	P=0.611N
Incidental Tumor Tests (d)	P=0.253N	P=0.465	P=0.351N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.511	P=0.490N
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/49 (8%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	9.2%	15.8%	12.4%
Terminal Rates (c)	1/39 (3%)	4/40 (10%)	2/28 (7%)
Week of First Observation	67	88	54
Life Table Tests (d)	P=0.387	P=0.294	P=0.483
Incidental Tumor Tests (d)	P=0.521N	P=0.229	P=0.617N
Cochran-Armitage Trend Test (d)	P=0.553N		
Fisher Exact Test (d)		P=0.274	P=0.631N
Integumentary System: Sarcoma or Fibrosarcoma			
Overall Rates (a)	4/49 (8%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	8.9%	8.8%	5.7%
Terminal Rates (c)	0/39 (0%)	1/40 (3%)	0/28 (0%)
Week of First Observation	67	88	54
Life Table Tests (d)	P=0.390N	P=0.611N	P=0.455N
Incidental Tumor Tests (d)	P=0.113N	P=0.643	P=0.153N
Cochran-Armitage Trend Test (d)	P=0.265N		
Fisher Exact Test (d)		P=0.631N	P=0.329N
Integumentary System: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/49 (10%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	11.2%	15.8%	12.4%
Terminal Rates (c)	1/39 (3%)	4/40 (10%)	2/28 (7%)
Week of First Observation	67	88	54
Life Table Tests (d)	P=0.510	P=0.414	P=0.605
Incidental Tumor Tests (d)	P=0.345N	P=0.349	P=0.402N
Cochran-Armitage Trend Test (d)	P=0.422N		
Fisher Exact Test (d)		P=0.394	P=0.487N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	14/49 (29%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	34.8%	22.5%	25.5%
Terminal Rates (c)	13/39 (33%)	9/40 (23%)	6/28 (21%)
Week of First Observation	67	104	50
Life Table Tests (d)	P=0.262N	P=0.150N	P=0.346N
Incidental Tumor Tests (d)	P=0.188N	P=0.207N	P=0.240N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.157N	P=0.103N

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

	Vehicle Control	375 mg/kg	750 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	4/49 (8%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	10.3%	15.0%	3.2%
Terminal Rates (c)	4/39 (10%)	6/40 (15%)	0/28 (0%)
Week of First Observation	104	104	100
Life Table Tests (d)	P=0.291N	P=0.384	P=0.291N
Incidental Tumor Tests (d)	P=0.269N	P=0.384	P=0.251N
Cochran-Armitage Trend Test (d)	P=0.161N		
Fisher Exact Test (d)		P=0.383	P=0.175N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	17/49 (35%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	42.3%	35.0%	27.9%
Terminal Rates (c)	16/39 (41%)	14/40 (35%)	6/28 (21%)
Week of First Observation	67	104	50
Life Table Tests (d)	P=0.198N	P=0.296N	P=0.245N
Incidental Tumor Tests (d)	P=0.132N	P=0.375N	P=0.146N
Cochran-Armitage Trend Test (d)	P=0.039N		
Fisher Exact Test (d)		P=0.308N	P=0.048N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/49 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.1%	10.0%	9.8%
Terminal Rates (c)	2/39 (5%)	4/40 (10%)	2/28 (7%)
Week of First Observation	104	104	89
Life Table Tests (d)	P=0.272	P=0.348	P=0.363
Incidental Tumor Tests (d)	P=0.333	P=0.348	P=0.457
Cochran-Armitage Trend Test (d)	P=0.426		
Fisher Exact Test (d)		P=0.348	P=0.509
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	2/49 (4%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	5.1%	15.0%	15.1%
Terminal Rates (c)	2/39 (5%)	6/40 (15%)	2/28 (7%)
Week of First Observation	104	104	89
Life Table Tests (d)	P=0.086	P=0.141	P=0.122
Incidental Tumor Tests (d)	P=0.152	P=0.141	P=0.246
Cochran-Armitage Trend Test (d)	P=0.195		
Fisher Exact Test (d)		P=0.141	P=0.226
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	5/49 (10%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	12.0%	10.0%	0.0%
Terminal Rates (c)	3/39 (8%)	4/40 (10%)	0/28 (0%)
Week of First Observation	76	104	
Life Table Tests (d)	P=0.058N	P=0.482N	P=0.069N
Incidental Tumor Tests (d)	P=0.044N	P=0.603N	P=0.040N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test (d)		P=0.487N	P=0.027N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	6/49 (12%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	14.4%	12.5%	0.0%
Terminal Rates (c)	4/39 (10%)	5/40 (13%)	0/28 (0%)
Week of First Observation	76	104	
Life Table Tests (d)	P=0.040N	P=0.480N	P=0.043N
Incidental Tumor Tests (d)	P=0.030N	P=0.590N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.016N		
Fisher Exact Test (d)		P=0.486N	P=0.013N

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

	Vehicle Control	375 mg/kg	750 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (e)	13/49 (27%)	14/49 (29%)	9/50 (18%)
Adjusted Rates (b)	32.4%	35.0%	30.9%
Terminal Rates (c)	12/39 (31%)	14/40 (35%)	8/28 (29%)
Week of First Observation	96	104	100
Life Table Tests (d)	P=0.518N	P=0.533	P=0.558N
Incidental Tumor Tests (d)	P=0.485N	P=0.541	P=0.506N
Cochran-Armitage Trend Test (d)	P=0.190N		
Fisher Exact Test (d)		P=0.500	P=0.218N
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	11/49 (22%)	11/49 (22%)	5/50 (10%)
Adjusted Rates (b)	25.4%	24.8%	14.9%
Terminal Rates (c)	7/39 (18%)	7/40 (18%)	2/28 (7%)
Week of First Observation	84	84	82
Life Table Tests (d)	P=0.225N	P=0.553N	P=0.245N
Incidental Tumor Tests (d)	P=0.054N	P=0.516N	P=0.063N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.595	P=0.079N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	20/49 (41%)	22/49 (45%)	13/50 (26%)
Adjusted Rates (b)	46.4%	49.8%	41.1%
Terminal Rates (c)	16/39 (41%)	18/40 (45%)	10/28 (36%)
Week of First Observation	84	84	82
Life Table Tests (d)	P=0.412N	P=0.474	P=0.430N
Incidental Tumor Tests (d)	P=0.198N	P=0.508	P=0.218N
Cochran-Armitage Trend Test (d)	P=0.076N		
Fisher Exact Test (d)		P=0.419	P=0.088N
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	4/45 (9%)	4/50 (8%)	2/44 (5%)
Adjusted Rates (b)	10.3%	10.0%	7.1%
Terminal Rates (c)	4/39 (10%)	4/40 (10%)	2/28 (7%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.421N	P=0.630N	P=0.497N
Incidental Tumor Tests (d)	P=0.421N	P=0.630N	P=0.497N
Cochran-Armitage Trend Test (d)	P=0.279N		
Fisher Exact Test (d)		P=0.582N	P=0.349N
Adrenal Capsule: Adenoma			
Overall Rates (e)	3/47 (6%)	0/46 (0%)	2/49 (4%)
Adjusted Rates (b)	7.9%	0.0%	7.4%
Terminal Rates (c)	3/38 (8%)	0/37 (0%)	2/27 (7%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.509N	P=0.126N	P=0.654N
Incidental Tumor Tests (d)	P=0.509N	P=0.126N	P=0.654N
Cochran-Armitage Trend Test (d)	P=0.376N		
Fisher Exact Test (d)		P=0.125N	P=0.480N
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.7%	2.5%	3.6%
Terminal Rates (c)	3/39 (8%)	1/40 (3%)	1/28 (4%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.283N	P=0.296N	P=0.429N
Incidental Tumor Tests (d)	P=0.283N	P=0.296N	P=0.429N
Cochran-Armitage Trend Test (d)	P=0.196N		
Fisher Exact Test (d)		P=0.301N	P=0.301N

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

	Vehicle Control	375 mg/kg	750 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	28/49 (57%)	27/50 (54%)	22/50 (44%)
Adjusted Rates (b)	68.1%	64.2%	70.5%
Terminal Rates (c)	26/39 (67%)	25/40 (63%)	19/28 (68%)
Week of First Observation	67	99	50
Life Table Tests (d)	P=0.389	P=0.437N	P=0.414
Incidental Tumor Tests (d)	P=0.535	P=0.478N	P=0.572
Cochran-Armitage Trend Test (d)	P=0.113N		
Fisher Exact Test (d)		P=0.456N	P=0.134N
All Sites: Malignant Tumors			
Overall Rates (a)	23/49 (47%)	29/50 (58%)	13/50 (26%)
Adjusted Rates (b)	48.9%	60.4%	34.4%
Terminal Rates (c)	15/39 (38%)	21/40 (53%)	4/28 (14%)
Week of First Observation	67	84	54
Life Table Tests (d)	P=0.270N	P=0.248	P=0.243N
Incidental Tumor Tests (d)	P=0.012N	P=0.154	P=0.007N
Cochran-Armitage Trend Test (d)	P=0.022N		
Fisher Exact Test (d)		P=0.184	P=0.025N
All Sites: All Tumors			
Overall Rates (a)	39/49 (80%)	40/50 (80%)	32/50 (64%)
Adjusted Rates (b)	83.0%	83.3%	84.0%
Terminal Rates (c)	31/39 (79%)	32/40 (80%)	22/28 (79%)
Week of First Observation	67	84	50
Life Table Tests (d)	P=0.266	P=0.554N	P=0.301
Incidental Tumor Tests (d)	P=0.253N	P=0.588	P=0.302N
Cochran-Armitage Trend Test (d)	P=0.047N		
Fisher Exact Test (d)		P=0.579	P=0.067N

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

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

Study	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Microbiological Associates			
d-Limonene	0/49	4/49	4/49
Benzyl alcohol	0/50	1/50	1/50
α-Methylbenzyl alcohol	1/49	5/49	6/49
TOTAL	1/148 (0.7%)	10/148 (6.8%)	11/148 (7.4%)
SD (b)	1.18%	4.27%	5.16%
Range (c)			
High	1/49	5/49	6/49
Low	0/50	1/50	1/50
Overall Historical Incidence			
TOTAL	22/2,091 (1.1%)	104/2,091 (5.0%)	124/2,091 (5.9%)
SD (b)	2.08%	4.20%	4.92%
Range (c)			
High	6/50	7/50	10/50
Low	0/50	0/50	0/50

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

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

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Abscess, NOS	1 (2%)	2 (4%)	
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Inflammation, granulomatous	2 (4%)		
Infection, fungal	1 (2%)		
Necrosis, fat			2 (4%)
Foreign material, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(44)	(50)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, serous	1 (2%)		
Inflammation, suppurative	2 (4%)	3 (7%)	1 (2%)
Inflammation, chronic	1 (2%)		
Foreign material, NOS	1 (2%)	1 (2%)	3 (6%)
#Lung	(49)	(50)	(50)
Congestion, NOS			7 (14%)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	6 (12%)
Sequestration		1 (2%)	
Inflammation, interstitial	1 (2%)		2 (4%)
Inflammation, acute			1 (2%)
Bronchopneumonia, chronic	1 (2%)		
Foreign material, NOS	1 (2%)		7 (14%)
Hemosiderosis	1 (2%)		
Hyperplasia, alveolar epithelium	1 (2%)		
Epithelialization	3 (6%)	1 (2%)	3 (6%)
#Lung/alveoli	(49)	(50)	(50)
Histiocytosis	2 (4%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Spleen	(48)	(49)	(48)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	
Hematopoiesis	4 (8%)	5 (10%)	1 (2%)
#Mandibular lymph node	(48)	(50)	(45)
Hemorrhage		1 (2%)	
Hyperplasia, plasma cell		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
#Mediastinal lymph node	(48)	(50)	(45)
Hemorrhage		1 (2%)	
#Mesenteric lymph node	(48)	(50)	(45)
Hemorrhage	21 (44%)	12 (24%)	8 (18%)
Degeneration, cystic	1 (2%)		
Angiectasis	1 (2%)		
#Renal lymph node	(48)	(50)	(45)
Hemorrhage			1 (2%)
#Lung	(49)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Liver	(49)	(49)	(50)
Hematopoiesis		3 (6%)	

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

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Peyer's patch	(43)	(48)	(40)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	
#Cecum	(45)	(48)	(41)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(42)	(34)	(41)
Cyst, NOS	3 (7%)	5 (15%)	
Depletion, lymphoid		1 (3%)	
CIRCULATORY SYSTEM			
#Brain	(49)	(50)	(50)
Embolus, septic	1 (2%)		
*Abdominal cavity	(49)	(50)	(50)
Polyangiitis	1 (2%)		
#Heart	(49)	(50)	(50)
Polyangiitis			1 (2%)
#Heart/atrium	(49)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Cardiac valve	(49)	(50)	(50)
Infection, bacterial	1 (2%)		
DIGESTIVE SYSTEM			
*Tooth	(49)	(50)	(50)
Dysplasia, NOS	10 (20%)	10 (20%)	
#Salivary gland	(48)	(50)	(50)
Lymphocytic inflammatory infiltrate	2 (4%)	3 (6%)	1 (2%)
Necrosis, NOS		1 (2%)	
#Liver	(49)	(49)	(50)
Cyst, NOS	1 (2%)		
Inflammation, multifocal	2 (4%)		
Fibrosis, multifocal		1 (2%)	
Necrosis, coagulative	1 (2%)		
Metamorphosis, fatty	1 (2%)	2 (4%)	
Cytoplasmic change, NOS	1 (2%)	3 (6%)	1 (2%)
Basophilic cyto change	1 (2%)		
Ground glass cyto change			1 (2%)
Eosinophilic cyto change			1 (2%)
#Liver/centrilobular	(49)	(49)	(50)
Necrosis, NOS	2 (4%)	1 (2%)	2 (4%)
Metamorphosis, fatty			1 (2%)
*Gallbladder	(49)	(50)	(50)
Dilatation, NOS			1 (2%)
Degeneration, hyaline	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
#Pancreas	(46)	(49)	(44)
Dilatation/ducts			1 (2%)
#Pancreatic acinus	(46)	(49)	(44)
Atypia, NOS		1 (2%)	
Atrophy, NOS			1 (2%)
#Glandular stomach	(46)	(50)	(44)
Ectopia		1 (2%)	
Inflammation, acute		1 (2%)	
Hyperplasia, epithelial			1 (2%)
#Forestomach	(46)	(50)	(44)
Ulcer, NOS		2 (4%)	2 (5%)
Inflammation, acute/chronic	8 (17%)	4 (8%)	2 (5%)
Inflammation, chronic	1 (2%)		1 (2%)
Hyperplasia, epithelial	11 (24%)	4 (8%)	4 (9%)
Hyperplasia, focal		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Small intestine	(43)	(48)	(40)
Hyperplasia, epithelial		1 (2%)	
#Duodenum	(43)	(48)	(40)
Inflammation, acute necrotizing		1 (2%)	
#Cecum	(45)	(48)	(41)
Hyperplasia, epithelial		2 (4%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Mineralization		1 (2%)	
Glomerulonephritis, NOS	2 (4%)	5 (10%)	1 (2%)
Pyelonephritis, NOS	1 (2%)	2 (4%)	
Lymphocytic inflammatory infiltrate	7 (14%)	1 (2%)	6 (12%)
Inflammation, interstitial		1 (2%)	
Fibrosis, focal		2 (4%)	
Fibrosis, diffuse			1 (2%)
#Renal papilla	(49)	(50)	(50)
Mineralization		1 (2%)	
#Urinary bladder	(49)	(49)	(47)
Calculus, gross observation only		1 (2%)	
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, papillary		1 (2%)	
*Urethral gland	(49)	(50)	(50)
Hemorrhage		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(42)	(48)
Cyst, NOS	1 (2%)	1 (2%)	
#Adrenal/capsule	(47)	(46)	(49)
Hyperplasia, focal	6 (13%)		2 (4%)
#Adrenal cortex	(47)	(46)	(49)
Hyperplasia, focal	1 (2%)		
#Thyroid	(46)	(49)	(50)
Ultimobranchial cyst			1 (2%)
Cystic follicles	1 (2%)		
Hyperplasia, follicular cell	3 (7%)	2 (4%)	
#Thyroid follicle	(46)	(49)	(50)
Atrophy, NOS		2 (4%)	
#Pancreatic islets	(46)	(49)	(44)
Hyperplasia, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*Preputial gland	(49)	(50)	(50)
Dilatation/ducts		4 (8%)	2 (4%)
Abscess, NOS		1 (2%)	1 (2%)
Inflammation, chronic		3 (6%)	1 (2%)
Hyperplasia, NOS			1 (2%)
#Prostate	(47)	(50)	(48)
Inflammation, suppurative			1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)	
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS			1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)
Hyperplasia, focal		1 (2%)	

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

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Testis	(49)	(50)	(49)
Mineralization	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic		1 (2%)	
Hypospermatogenesis	4 (8%)	5 (10%)	1 (2%)
*Epididymis	(49)	(50)	(50)
Granuloma, spermatic	1 (2%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Brain	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
#Brain/thalamus	(49)	(50)	(50)
Calculus, microscopic examination	19 (39%)	17 (34%)	23 (46%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)		
*Middle ear	(49)	(50)	(50)
Abscess, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Maxilla	(49)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Skeletal muscle	(49)	(50)	(50)
Mineralization			1 (2%)
BODY CAVITIES			
*Thoracic cavity	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
*Abdominal cavity	(49)	(50)	(50)
Hemorrhage	1 (2%)		
Necrosis, fat	5 (10%)		1 (2%)
*Pleura	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
*Epicardium	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Mesentery	(49)	(50)	(50)
Necrosis, fat		2 (4%)	
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate	35 (71%)	38 (76%)	21 (42%)
Amyloidosis	1 (2%)	1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			2
Animal missexed/no necropsy	1		

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

APPENDIX D

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

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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)
Fibroma	1 (2%)		
Fibrosarcoma		1 (2%)	
Lipoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(4)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	1 (25%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)		
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	3 (6%)	6 (12%)	
Malignant lymphoma, undifferentiated type	2 (4%)		1 (2%)
Malignant lymphoma, lymphocytic type	3 (6%)	1 (2%)	2 (4%)
Malignant lymphoma, mixed type	7 (14%)	2 (4%)	6 (12%)
Leukemia, NOS		1 (2%)	
#Spleen	(49)	(15)	(49)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(4)	(50)
Hemangiosarcoma			1 (2%)
*Mesentery	(50)	(50)	(50)
Hemangioma	1 (2%)		
#Uterus	(50)	(44)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(6)	(50)
Hepatocellular adenoma	1 (2%)	1 (17%)	
Hepatocellular carcinoma	1 (2%)		
#Forestomach	(50)	(48)	(48)
Squamous cell papilloma	3 (6%)	5 (10%)	4 (8%)
#Duodenum	(47)	(6)	(48)
Adenomatous polyp, NOS			2 (4%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(4)	(48)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	4 (8%)		6 (13%)
#Adrenal	(49)	(4)	(50)
Cortical adenoma	1 (2%)		
Pheochromocytoma	1 (2%)		
Pheochromocytoma, malignant	1 (2%)		

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(4)	(49)
Follicular cell adenoma	1 (2%)		3 (6%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
*Vagina	(50)	(50)	(50)
Leiomyoma		1 (2%)	
#Uterus	(50)	(44)	(50)
Leiomyosarcoma		1 (2%)	1 (2%)
#Uterus/endometrium	(50)	(44)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Ovary	(49)	(20)	(48)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain stem	(50)	(4)	(50)
Carcinoma, NOS, invasive	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
*Muscle of back	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Leiomyoma			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)
Sarcoma, NOS, uncertain primary or metastatic	1 (2%)		
Leiomyosarcoma, metastatic		1 (2%)	
Lower leg			
Sarcoma, NOS, uncertain primary or metastatic	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	9	7
Moribund sacrifice	1		
Terminal sacrifice	40	40	38
Dosing accident		1	5

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

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	33	23	24
Total primary tumors	49	25	33
Total animals with benign tumors	16	10	16
Total benign tumors	21	10	21
Total animals with malignant tumors	22	15	12
Total malignant tumors	25	15	12
Total animals with secondary tumors##	2	1	
Total secondary tumors	2	1	
Total animals with tumors-- uncertain benign or malignant	1		
Total uncertain tumors	1		
Total animals with tumors-- uncertain primary or metastatic	2		
Total uncertain tumors	2		

* 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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL ALCOHOL: VEHICLE CONTROL

ANIMAL NUMBER	C 3 1	C 2 3	C 1 7	C 2 4	C 1 1	C 4 5	C 0 3	C 0 6	C 2 6	C 0 1	C 0 2	C 0 4	C 0 5	C 0 7	C 0 8	C 0 9	C 1 0	C 1 2	C 1 3	C 1 4	C 1 5	C 1 6	C 1 8	C 1 9	C 2 0
WEEKS ON STUDY	0 4 2	0 6 9	0 7 8	0 8 5	1 0 0	1 0 0	1 0 1	1 0 2	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	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lipoma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										X
Alveolar/bronchiolar carcinoma																X							X		
Osteosarcoma, metastatic		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																						X			
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X	X				
Small intestine	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																					X			X	
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma													X												
Pheochromocytoma																									
Pheochromocytoma, malignant								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	−	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
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

+: Tissue examined microscopically
−: Required tissue not examined microscopicaliy
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 2 1	C 2 2	C 2 5	C 2 7	C 2 8	C 2 9	C 3 0	C 3 2	C 3 3	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 1	C 4 2	C 4 3	C 4 4	C 4 6	C 4 7	C 4 8	C 4 9	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																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																						X				1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X									X	X								5
Alveolar/bronchiolar carcinoma																										2
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X						1
Hepatocellular carcinoma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																X										1
Adenoma, NOS										X		X														4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Pheochromocytoma								X																		1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	+	+	+	+	–	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	*50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor				X																						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																X										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															2

* Animals necropsied

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

ANIMAL NUMBER	C031	C023	C017	C024	C011	C045	C003	C006	C026	C001	C002	C004	C005	C007	C008	C009	C010	C012	C013	C014	C015	C016	C018	C019	C020
WEEKS ON STUDY	042	069	078	085	100	100	101	102	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma		X																							
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS						X																			
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
Hemangioma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, unclear primary or metastatic			X																						
Malignant lymphoma, NOS						X	X																		
Malignant lymphoma, undifferentiated type					X																			X	
Malignant lymphoma, lymphocytic type																			X						
Malignant lymphoma, mixed type															X	X									
Lower leg, NOS																									
Sarcoma, NOS, unclear primary or metastatic						X																			

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

ANIMAL NUMBER	C 2 1	C 2 2	C 2 5	C 2 7	C 2 8	C 2 9	C 3 0	C 3 2	C 3 3	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 1	C 4 2	C 4 3	C 4 4	C 4 6	C 4 7	C 4 8	C 4 9	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
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
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
Hemangioma																	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
Sarcoma, NOS, unclear primary or meta																										1
Malignant lymphoma, NOS																		X								3
Malig. lymphoma, undifferent type																										2
Malig. lymphoma, lymphocytic type				X																					X	3
Malignant lymphoma, mixed type	X								X				X						X	X						7
Lower leg, NOS																										
Sarcoma, NOS, unclear primary or meta																										1

* Animals necropsied

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

ANIMAL NUMBER	C 0 9	C 4 3	C 0 1	C 0 8	C 1 4	C 4 6	C 1 7	C 2 1	C 2 3	C 0 2	C 0 3	C 0 4	C 0 5	C 0 6	C 0 7	C 1 0	C 1 1	C 1 2	C 1 3	C 1 5	C 1 6	C 1 8	C 1 9	C 2 0	C 2 2
WEEKS ON STUDY	0 2 1	0 7 1	0 8 7	0 8 9	0 9 3	0 9 8	1 0 1	1 0 1	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
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
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Alveolar/bronchiolar adenoma			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	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																		X					X		
Small intestine	+	+	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Large intestine	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Urinary bladder	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Adrenal	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
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
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
Leiomyoma																									
Uterus	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Adenocarcinoma, NOS																									
Leiomyosarcoma		X																							
Hemangiosarcoma																									
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
Leiomyosarcoma, metastatic		X																							
Malignant lymphoma, NOS			X	X		X		X														X			
Malignant lymphoma, lymphocytic type							X																		
Malignant lymphoma, mixed type									X																
Leukemia, NOS												X													

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

ANIMAL NUMBER	C 2 4	C 2 5	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 1	C 3 2	C 3 3	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 1	C 4 2	C 4 4	C 4 5	C 4 7	C 4 8	C 4 9	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																										
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	*50
Fibrosarcoma		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Alveolar/bronchiolar adenoma																										1
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Nasal cavity	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	2
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Spleen	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	−	−	−	−	15
Lymph nodes	+	−	−	+	−	−	−	+	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	15
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	5
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	9
Liver	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
Hepatocellular adenoma																										1
Bile duct	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Stomach	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma														X			X	X								5
Small intestine	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	6
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
URINARY SYSTEM																										
Kidney	−	+	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	9
Urinary bladder	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Adrenal	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Thyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
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
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
Leiomyoma					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, NOS											X															1
Leiomyosarcoma																										1
Hemangiosarcoma																X										1
Ovary	+	−	−	−	+	−	−	+	+	−	+	+	+	−	−	−	+	−	+	−	+	+	−	−	−	20
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	4
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
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
Leiomyosarcoma, metastatic																										1
Malignant lymphoma, NOS	X																									6
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type				X																						2
Leukemia, NOS																										1

* Animals necropsied

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

ANIMAL NUMBER	C 19	C 33	C 48	C 17	C 22	C 13	C 50	C 16	C 01	C 11	C 25	C 42	C 02	C 03	C 04	C 05	C 06	C 07	C 08	C 09	C 10	C 12	C 14	C 15	C 18
WEEKS ON STUDY	001	001	007	016	067	076	076	077	079	083	084	087	104	104	104	104	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	−	−	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	N	+	+	N	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Squamous cell papilloma																									X
Small intestine	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																					X				X
Large intestine	+	+	+	+	−	+	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X							X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									X
Parathyroid	+	−	−	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	−	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
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																									
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
Leiomyoma																									
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
Histiocytic sarcoma							X																		
Malignant lymphoma, undifferentiated type																								X	
Malignant lymphoma, lymphocytic type									X											X					
Malignant lymphoma, mixed type															X				X						X

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

ANIMAL NUMBER	C 2 0	C 2 1	C 2 3	C 2 4	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 1	C 3 2	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 1	C 4 3	C 4 4	C 4 5	C 4 6	C 4 7	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
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X							X				X									4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma														X					X						X	4
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenomatous polyp, NOS																										2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Adenoma, NOS								X												X			X			6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X								X															3
Parathyroid	+	+	+	+	−	+	+	−	+	−	−	+	+	−	+	+	+	−	+	+	+	+	+	+	−	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																X										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
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																										
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
Leiomyoma																								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
Histiocytic sarcoma																										1
Malignant lymphoma, undifferent type																										1
Malignant lymphoma, lymphocytic type																										2
Malignant lymphoma, mixed type														X				X				X				6

* Animals necropsied

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

	Vehicle Control	375 mg/kg	750 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	(b) 1/4 (25%)	4/50 (8%)
Adjusted Rates (c)	12.2%		10.5%
Terminal Rates (d)	5/41 (12%)		4/38 (11%)
Week of First Observation	104		104
Life Table Test (e)			P=0.548N
Incidental Tumor Test (e)			P=0.548N
Fisher Exact Test (e)			P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	(b) 1/4 (25%)	4/50 (8%)
Adjusted Rates (c)	17.1%		10.5%
Terminal Rates (d)	7/41 (17%)		4/38 (11%)
Week of First Observation	104		104
Life Table Test (e)			P=0.305N
Incidental Tumor Test (e)			P=0.305N
Fisher Exact Test (e)			P=0.263N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (f)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (c)	7.3%	2.3%	4.9%
Terminal Rates (d)	3/41 (7%)	0/41 (0%)	1/38 (3%)
Week of First Observation	104	101	79
Life Table Tests (e)	P=0.436N	P=0.307N	P=0.538N
Incidental Tumor Tests (e)	P=0.429N	P=0.307N	P=0.416N
Cochran-Armitage Trend Test (e)	P=0.399N		
Fisher Exact Test (e)		P=0.309N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (f)	8/50 (16%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (c)	19.5%	4.8%	15.8%
Terminal Rates (d)	8/41 (20%)	1/41 (2%)	6/38 (16%)
Week of First Observation	104	103	104
Life Table Tests (e)	P=0.360N	P=0.048N	P=0.445N
Incidental Tumor Tests (e)	P=0.417N	P=0.049N	P=0.445N
Cochran-Armitage Trend Test (e)	P=0.314N		
Fisher Exact Test (e)		P=0.046N	P=0.387N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	16/50 (32%)	9/50 (18%)	9/50 (18%)
Adjusted Rates (c)	36.2%	19.1%	22.9%
Terminal Rates (d)	13/41 (32%)	3/41 (7%)	8/38 (21%)
Week of First Observation	100	87	79
Life Table Tests (e)	P=0.109N	P=0.101N	P=0.135N
Incidental Tumor Tests (e)	P=0.166N	P=0.049N	P=0.243N
Cochran-Armitage Trend Test (e)	P=0.060N		
Fisher Exact Test (e)		P=0.083N	P=0.083N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (f)	16/50 (32%)	10/50 (20%)	9/50 (18%)
Adjusted Rates (c)	36.2%	21.2%	22.9%
Terminal Rates (d)	13/41 (32%)	4/41 (10%)	8/38 (21%)
Week of First Observation	100	87	79
Life Table Tests (e)	P=0.112N	P=0.147N	P=0.135N
Incidental Tumor Tests (e)	P=0.170N	P=0.084N	P=0.243N
Cochran-Armitage Trend Test (e)	P=0.062N		
Fisher Exact Test (e)		P=0.127N	P=0.083N

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

	Vehicle Control	375 mg/kg	750 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (f)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (c)	7.3%	12.2%	10.5%
Terminal Rates (d)	3/41 (7%)	5/41 (12%)	4/38 (11%)
Week of First Observation	104	104	104
Life Table Tests (e)	P=0.383	P=0.356	P=0.458
Incidental Tumor Tests (e)	P=0.383	P=0.356	P=0.458
Cochran-Armitage Trend Test (e)	P=0.427		
Fisher Exact Test (e)		P=0.357	P=0.500
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	(b) 0/4 (0%)	6/48 (13%)
Adjusted Rates (c)	9.8%		16.2%
Terminal Rates (d)	4/41 (10%)		6/37 (16%)
Week of First Observation	104		104
Life Table Test (e)			P=0.305
Incidental Tumor Test (e)			P=0.305
Fisher Exact Test (e)			P=0.344
Anterior Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	(b) 0/4 (0%)	6/48 (13%)
Adjusted Rates (c)	12.2%		16.2%
Terminal Rates (d)	5/41 (12%)		6/37 (16%)
Week of First Observation	104		104
Life Table Test (e)			P=0.428
Incidental Tumor Test (e)			P=0.428
Fisher Exact Test (e)			P=0.471
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/50 (2%)	(b) 0/4 (0%)	3/49 (6%)
Adjusted Rates (c)	2.4%		8.1%
Terminal Rates (d)	1/41 (2%)		3/37 (8%)
Week of First Observation	104		104
Life Table Test (e)			P=0.269
Incidental Tumor Test (e)			P=0.269
Fisher Exact Test (e)			P=0.301
All Sites: Benign Tumors			
Overall Rates (f)	16/50 (32%)	10/50 (20%)	16/50 (32%)
Adjusted Rates (c)	39.0%	23.6%	42.1%
Terminal Rates (d)	16/41 (39%)	9/41 (22%)	16/38 (42%)
Week of First Observation	104	87	104
Life Table Tests (e)	P=0.447	P=0.122N	P=0.480
Incidental Tumor Tests (e)	P=0.491	P=0.107N	P=0.480
Cochran-Armitage Trend Test (e)	P=0.544		
Fisher Exact Test (e)		P=0.127N	P=0.585
All Sites: Malignant Tumors			
Overall Rates (f)	22/50 (44%)	15/50 (30%)	12/50 (24%)
Adjusted Rates (c)	45.7%	31.2%	29.7%
Terminal Rates (d)	15/41 (37%)	8/41 (20%)	10/38 (26%)
Week of First Observation	42	71	76
Life Table Tests (e)	P=0.059N	P=0.141N	P=0.072N
Incidental Tumor Tests (e)	P=0.060N	P=0.093N	P=0.136N
Cochran-Armitage Trend Test (e)	P=0.021N		
Fisher Exact Test (e)		P=0.107N	P=0.028N

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

	Vehicle Control	375 mg/kg	750 mg/kg
All Sites: All Tumors			
Overall Rates (f)	33/50 (66%)	23/50 (46%)	24/50 (48%)
Adjusted Rates (c)	67.3%	47.8%	59.8%
Terminal Rates (d)	25/41 (61%)	16/41 (39%)	22/38 (58%)
Week of First Observation	42	71	76
Life Table Tests (e)	P=0.132N	P=0.067N	P=0.150N
Incidental Tumor Tests (e)	P=0.134N	P=0.037N	P=0.234N
Cochran-Armitage Trend Test (e)	P=0.044N		
Fisher Exact Test (e)		P=0.035N	P=0.053N

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

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF α-METHYLBENZYL 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)
Ulcer, NOS	1 (2%)		
Inflammation, chronic	2 (4%)	2 (4%)	
Acanthosis		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(2)	(50)
Hemorrhage			2 (4%)
Inflammation, serous	1 (2%)		
Inflammation, suppurative	8 (16%)		3 (6%)
Foreign material, NOS	9 (18%)		7 (14%)
#Lung	(50)	(4)	(50)
Congestion, NOS			7 (14%)
Edema, NOS			1 (2%)
Hemorrhage	3 (6%)	1 (25%)	7 (14%)
Inflammation, interstitial	3 (6%)		
Perivascular cuffing	3 (6%)		1 (2%)
Foreign material, NOS			1 (2%)
Hemosiderosis	1 (2%)		
Epithelialization	1 (2%)		
#Lung/alveoli	(50)	(4)	(50)
Histiocytosis	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#Spleen	(49)	(15)	(49)
Fibrosis			1 (2%)
Necrosis, NOS			1 (2%)
Hyperplasia, lymphoid		2 (13%)	1 (2%)
Hematopoiesis	4 (8%)	2 (13%)	
#Mandibular lymph node	(48)	(15)	(49)
Hemosiderosis	1 (2%)		
Plasmacytosis		2 (13%)	
#Cervical lymph node	(48)	(15)	(49)
Plasmacytosis	1 (2%)		
#Abdominal lymph node	(48)	(15)	(49)
Plasmacytosis	1 (2%)		
#Mesenteric lymph node	(48)	(15)	(49)
Hemorrhage	1 (2%)	2 (13%)	1 (2%)
Degeneration, cystic		1 (7%)	
#Renal lymph node	(48)	(15)	(49)
Plasmacytosis		1 (7%)	
*Bone	(50)	(50)	(50)
Myelofibrosis	1 (2%)		
*Skull	(50)	(50)	(50)
Myelofibrosis	18 (36%)		24 (48%)
*Femur	(50)	(50)	(50)
Myelofibrosis	16 (32%)		20 (40%)
*Tibia	(50)	(50)	(50)
Myelofibrosis			1 (2%)
#Liver	(50)	(6)	(50)
Hematopoiesis	2 (4%)		
#Thymus	(46)	(5)	(43)
Cyst, NOS	1 (2%)		1 (2%)

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

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
*Abdominal cavity	(50)	(50)	(50)
Polyangiitis	1 (2%)		1 (2%)
#Urinary bladder	(49)	(3)	(48)
Polyangiitis			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	1 (2%)		
#Salivary gland	(49)	(9)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (11%)	2 (4%)
#Liver	(50)	(6)	(50)
Inflammation, multifocal			2 (4%)
Bacterial septicemia			1 (2%)
Necrosis, coagulative			2 (4%)
Metamorphosis, fatty	1 (2%)		
Basophilic cyto change			1 (2%)
Hyperplasia, focal			1 (2%)
#Esophagus	(50)	(4)	(50)
Necrosis, NOS			1 (2%)
#Forestomach	(50)	(48)	(48)
Ulcer, NOS	3 (6%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	8 (16%)	5 (10%)	7 (15%)
Inflammation, chronic	2 (4%)		
Erosion			1 (2%)
Hyperplasia, epithelial	6 (12%)	7 (15%)	9 (19%)
Hyperplasia, focal		1 (2%)	
#Duodenum	(47)	(6)	(48)
Hyperplasia, epithelial		1 (17%)	
URINARY SYSTEM			
#Kidney	(50)	(9)	(50)
Cyst, NOS	1 (2%)		
Glomerulonephritis, NOS	1 (2%)	1 (11%)	
Lymphocytic inflammatory infiltrate	2 (4%)		4 (8%)
Inflammation, interstitial			2 (4%)
Nephropathy			1 (2%)
Nephrosis, NOS	1 (2%)		
Amyloidosis	1 (2%)		1 (2%)
#Urinary bladder	(49)	(3)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(4)	(48)
Focal cellular change			2 (4%)
Hyperplasia, focal	1 (2%)		
Angiectasis	2 (4%)		1 (2%)
#Adrenal	(49)	(4)	(50)
Bacterial septicemia			1 (2%)
Degeneration, lipoid	1 (2%)		1 (2%)
Necrosis, coagulative			1 (2%)
#Adrenal/capsule	(49)	(4)	(50)
Hyperplasia, focal	4 (8%)		3 (6%)
#Adrenal cortex	(49)	(4)	(50)
Hypertrophy, focal			1 (2%)
#Thyroid	(50)	(4)	(49)
Cystic follicles			1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, follicular cell	4 (8%)		7 (14%)

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

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(47)	(4)	(48)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Vagina	(50)	(50)	(50)
Inflammation, suppurative			2 (4%)
Inflammation, chronic		1 (2%)	
Cholesterol deposit	1 (2%)		
#Uterus	(50)	(44)	(50)
Hydrometra			1 (2%)
Hemorrhage			1 (2%)
Inflammation, suppurative		2 (5%)	1 (2%)
#Uterus/endometrium	(50)	(44)	(50)
Hyperplasia, cystic	39 (78%)	41 (93%)	41 (82%)
#Ovary	(49)	(20)	(48)
Follicular cyst, NOS	2 (4%)	2 (10%)	2 (4%)
Parovarian cyst	9 (18%)	10 (50%)	5 (10%)
Hemorrhagic cyst			1 (2%)
Abscess, NOS	3 (6%)	3 (15%)	
NERVOUS SYSTEM			
#Intracranial arachnoid	(50)	(4)	(50)
Hyperplasia, NOS			1 (2%)
#Brain	(50)	(4)	(50)
Hemorrhage			1 (2%)
#Brain/thalamus	(50)	(4)	(50)
Calculus, microscopic examination	15 (30%)	2 (50%)	19 (38%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Phthisis bulbi	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat	1 (2%)	1 (2%)	3 (6%)
Hemosiderosis			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	34 (68%)	2 (4%)	33 (66%)
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

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

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. 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	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) (12,18 mo) *M. pul. (Mycoplasma pulmonis)* (18 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	*M. pul.* (18 mo)

Results

Results are presented in Table E1.

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

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	8/9	RCV
12	--	None positive
18	5/8	*M. pul.* (b)
MICE		
6	--	None positive
12	--	None positive
18	1/3	*M. pul.*

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

APPENDIX F

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

Pelleted Diet: April 1981 to April 1983

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.8 ± 0.87	22.2-25.3	24
Crude fat (percent by weight)	5.0 ± 0.45	4.2-5.7	24
Crude fiber (percent by weight)	3.3 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.4 ± 0.37	5.7-7.1	24
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,929 ± 2,683	3,600-18,000	24
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.4 ± 2.17	13.0-21.0	(b) 23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.20	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302 ± 120	3,200-3,430	4
Minerals			
Calcium (percent)	1.21 ± 0.15	0.72-1.53	24
Phosphorus (percent)	0.97 ± 0.04	0.88-1.1	24
Potassium (percent)	0.862 ± 0.10	0.772-0.970	3
Chloride (percent)	0.546 ± 0.10	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-99.4	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four lots of feed analyzed for nutrients reported in this table were manufactured during 1983-1985.
(b) One lot (July 22, 1981) was not analyzed for thiamine.

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.46 ± 0.10	<0.29-0.70	24
Cadmium (ppm)	<0.1		24
Lead (ppm)	0.95 ± 0.76	0.33-3.37	24
Mercury (ppm) (a)	<0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (b)	<10	<5-<10	24
Nitrate nitrogen (ppm) (c)	10.24 ± 4.1	3.8-22.0	24
Nitrite nitrogen (ppm) (c)	2.0 ± 1.6	<0.4-6.9	24
BHA (ppm) (d)	6.1 ± 4.9	<0.4-17.0	24
BHT (ppm) (d)	3.3 ± 2.6	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	39,879 ± 27,920	4,900-88,000	24
Coliform (MPN/g) (f)	15.5 ± 22.7	<3.0-93	23
Coliform (MPN/g) (g)	34.0 ± 93.4	<3.0-460	24
E. coli (MPN/g) (h)	<3		24
Total nitrosamines (ppb) (i,j)	3.7 ± 2.7	0.8-9.3	23
Total nitrosamines (ppb) (j,k)	15.2 ± 56.4	0.8-279.5	24
N-Nitrosodimethylamine (ppb) (j,l)	2.7 ± 2.5	0.8-8.3	23
N-Nitrosodimethylamine (ppb) (j,m)	14.1 ± 56.3	0.8-278.0	24
N-Nitrosopyrrolidine (ppb)	1.2 ± 0.5	<0.9-2.9	24
Pesticides (ppm)			
α-BHC (a,n)	<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 (o)	<0.05	0.09	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 (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (p)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a,q)	<0.01		18
Endosulfan II (a,q)	<0.01		18
Endosulfan sulfate (a,q)	<0.03		18

TABLE F4. 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) Detection limit was reduced from 10 ppb to 5 ppb after July 1981.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) Mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained for the lot produced on September 23, 1982; MPN = most probable number.
(g) Mean, standard deviation, and range include the value given in footnote (f).
(h) All values were less than 3 MPN/g.
(i) Mean, standard deviation, and range exclude one very high value of 279.5 ppb obtained for the lot produced on April 27, 1981.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range include the value given in footnote (i).
(l) Mean, standard deviation, and range exclude one very high value of 278 ppb obtained for the lot produced on April 27, 1981.
(m) Mean, standard deviation, and range include the value given in footnote (l).
(n) BHC is hexachlorocyclohexane or benzene hexachloride.
(o) One observation, on August 26, 1981, was above the detection limit.
(p) Ten lots contained more than 0.05 ppm.
(q) Six lots were not analyzed for this pesticide.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF α-METHYLBENZYL ALCOHOL FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of α-Methylbenzyl Alcohol

Food-grade α-methylbenzyl alcohol was obtained as a colorless liquid in two lots from Givaudan Corporation (Clifton, NJ) (Table G1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the α-methylbenzyl alcohol studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as α-methylbenzyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. For both lots, all spectra were consistent with those expected from the structure and with literature spectra (Sadtler Standard Spectra). Representative infrared and nuclear magnetic resonance spectra are presented in Figures G1 and G2.

The purity of each lot was determined by elemental analysis, Karl Fischer water analysis, determination of ketone concentration by reaction of the study material with an alkaline solution of hydroxylamine hydrochloride followed by back-titration with 0.1 N or 0.5 N hydrochloric acid, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed with silica gel plates and two solvent systems, chloroform (solvent system 1) and hexanes:acetone (85:15) (solvent system 2), and with a chromic acid-sulfuric acid spray reagent and 254 nm visualization. Gas chromatographic analysis was performed with flame ionization detection, a nitrogen carrier at 50 ml/minute, and either a 1% SP1240 column (system 1) or a 10% Carbowax 20M TPA column (system 2).

The results of elemental analysis of lot no. 50839 for carbon and hydrogen were in agreement with the theoretical values. Lot no. 50839 contained 0.04% water and 0.05% ketone impurities (as acetophenone). Thin-layer chromatography detected two slight trace impurities by solvent system 1 and one slight trace impurity by solvent system 2. Gas chromatographic system 1 detected 11 impurities with a total relative area of 0.42%. Gas chromatography with system 2 detected 17 impurities with a total relative area of 0.58%; 3 of the impurities had relative areas of 0.11%, 0.11%, and 0.09%. Cumulative data indicated that lot no. 50839 was greater than 99% pure and met Food Chemical Codex specifications for assay, total ketone impurities, specific gravity, and refractive index.

TABLE G1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
50839	50839	50839	50839; 68637
Date of Initial Use			
11/7/79	2/5/80	5/19/80	50839--4/6/81; 68637--9/16/82
Supplier			
Givaudan Corporation (Clifton, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

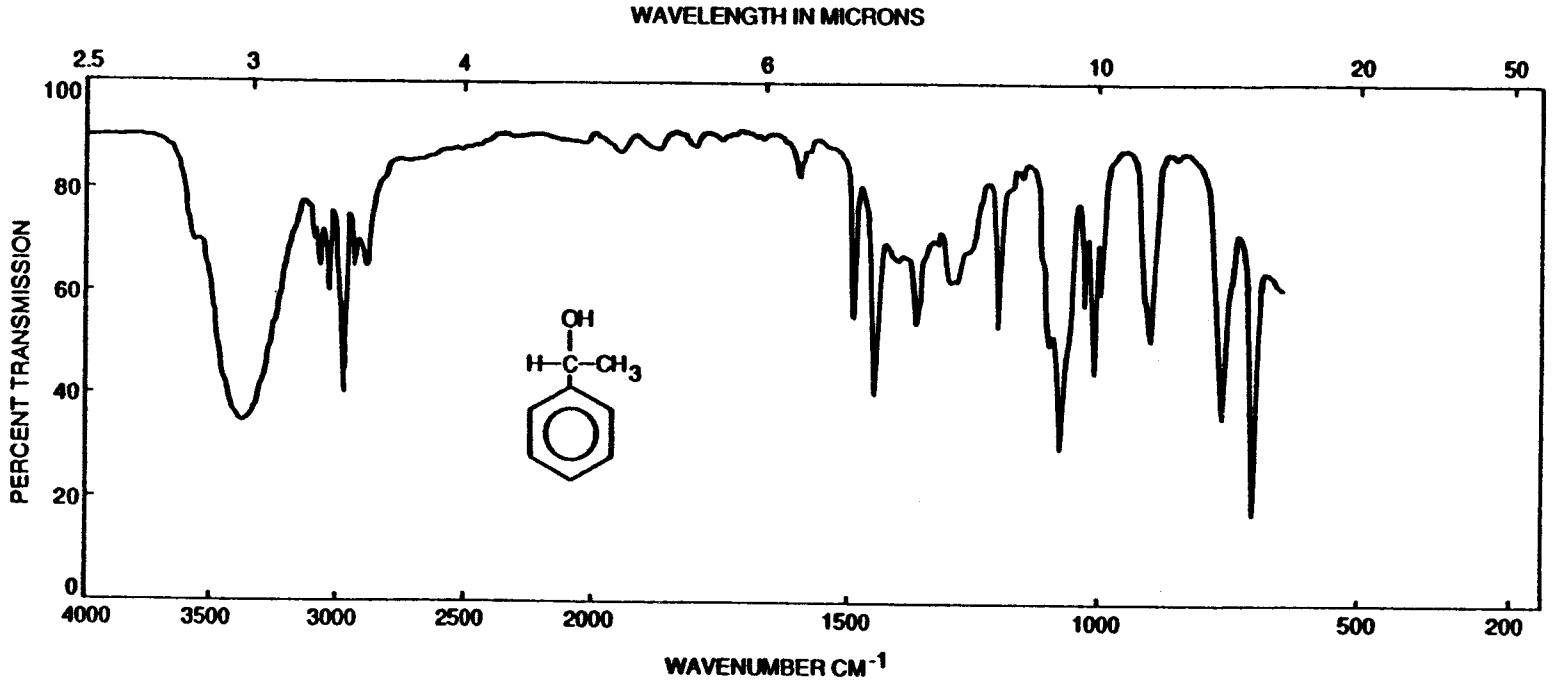

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF α-METHYLBENZYL ALCOHOL (LOT NO. 50839)

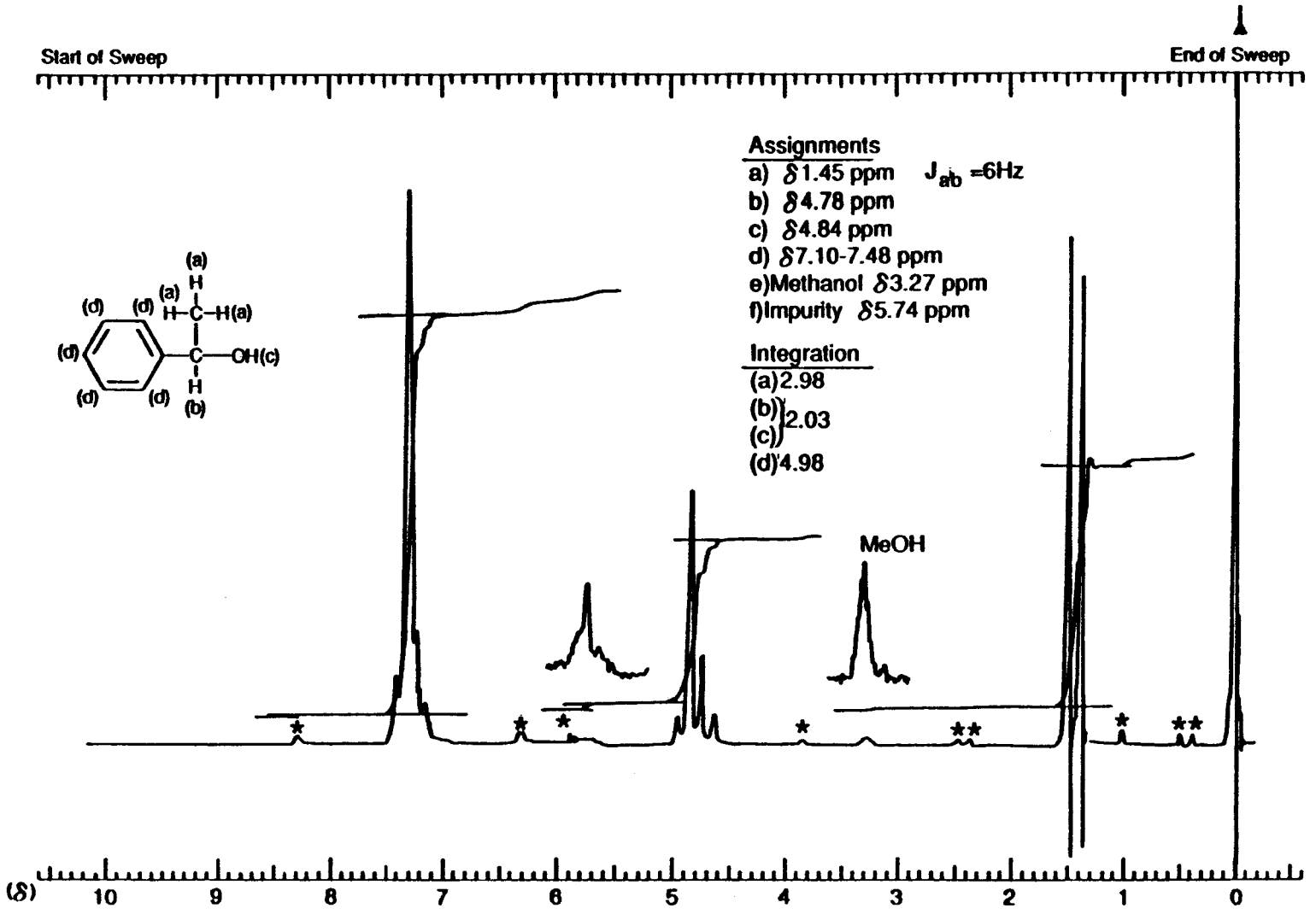

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF α-METHYLBENZYL ALCOHOL (LOT NO. 50839)

The results of elemental analysis of lot no. 68637 for carbon and hydrogen were in agreement with the theoretical values. Lot no. 68637 contained 0.14% water and 0.32% ketone impurities (as acetophenone). One slight trace impurity was detected by each of the two thin-layer chromatographic systems. Both gas chromatographic systems detected one impurity, tentatively identified by system 2 as acetophenone, with a relative area of 0.16% by system 1 and 0.10% by system 2. Cumulative data indicated that lot no. 68637 was greater than 99% pure.

Stability studies performed by gas chromatography with the same system as that described before for system 1, and with the injected sample containing 1.2% by volume of undecyl alcohol as an internal standard, indicated that α-methylbenzyl alcohol was stable as a bulk chemical when stored protected from light for 2 weeks at temperatures up to 60° C. Confirmation of the stability of the bulk chemical during the 2-year studies (lot no. 68637, 1 year after the original analysis) was obtained by gas chromatography. The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

Preparation and Characterization of Dose Mixtures

α-Methylbenzyl alcohol and corn oil were mixed to give the desired concentrations (Table G2). The stability of α-methylbenzyl alcohol in corn oil (1% concentration w/v) was determined by performing gas chromatography with a 20% SP2100 + 0.1% Carbowax 1500 column and flame ionization detection on methanol extracts of corn oil solutions; heptyl alcohol was used as the internal standard. α-Methylbenzyl alcohol, dissolved in corn oil at 10 mg/ml, was found by the analytical chemistry laboratory to be stable at room temperature in the dark for 7 days. The study laboratory found that the compound, dissolved at 4.96 mg/ml or 150 mg/ml, was stable when stored at room temperature for 14 days. Dose mixtures were stored no longer than 15 days at 4° C for the 13-week studies and for no longer than 3 weeks at 5° C for the 2-year studies.

TABLE G2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Appropriate weight of chemical weighed into volumetric flask. Corn oil added to volume. Flask stoppered and contents shaken until mixed	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Maximum Storage Time			
24 h	8 d	15 d	3 wk
Storage Conditions			
Room temperature	Room temperature	4° C	5° C

APPENDIX G. CHEMICAL CHARACTERIZATION

Periodic analyses of formulated α-methylbenzyl alcohol mixtures were conducted at the study laboratory and the analytical chemistry laboratory by gas chromatography with the same procedure as described for the stability studies. Dose mixtures were analyzed one time during the 13-week studies (Table G3). The results of the analysis indicated that all the doses were within ±1% of the target concentrations.

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the α-methylbenzyl alcohol studies, all 42 mixtures analyzed were formulated within ±10% of the target concentrations (Table G4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table G5).

TABLE G3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Date Mixed	Concentration of α-Methylbenzyl Alcohol in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
07/09/80	4.69	4.70	100.21
	9.38	9.38	100.00
	18.75	18.76	100.05
	37.5	37.33	99.47
	75	74.98	99.97
	150	149.99	99.99
	300	300.02	99.99

(a) Results of duplicate analysis

TABLE G4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Date Mixed	Concentration of α-Methylbenzyl Alcohol in Corn Oil for Target Concentration (mg/ml) (a)		
	37.5	75	150
04/02/81	39.3	72.5	
04/16/81		81.8	162
05/28/81	35.4	74.3	162
07/23/81	38.6	79.0	156
09/17/81	37.1	73.7	150
11/12/81	39.2	78.5	158
01/07/82	38.3	75.5	152
03/04/82	38.3	73.1	140
04/29/82	39.0	74.9	154
06/24/82	38.3	71.4	144
08/19/82	36.9	73.8	147
10/14/82	36.0	73.8	146
12/09/82	36.3	73.0	146
02/03/83	37.9	73.8	144
03/30/83		74.7	143
Mean (mg/ml)	37.7	74.9	150
Standard deviation	1.28	2.78	7.2
Coefficient of variation (percent)	3.4	3.7	4.8
Range (mg/ml)	35.4-39.3	71.4-81.8	140-162
Number of samples	13	15	14

(a) Results of duplicate analysis

TABLE G5. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF α-METHYLBENZYL ALCOHOL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
04/02/81	37.5	39.29	37.02
11/12/81	150.0	157.8	146.7
06/24/82	75.0	71.4	73.7
12/09/82	37.5	36.3	36.1
03/30/83	75.0	74.7	74.6

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

APPENDIX H

GENETIC TOXICOLOGY

OF α-METHYLBENZYL ALCOHOL

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1987) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in four strains. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 6.7 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 1.5 µg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

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

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

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

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

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

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

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

RESULTS

α-Methylbenzyl alcohol was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested at concentrations up to 6,666 μg/plate with a preincubation protocol in the presence or absence of 10% Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 mix (Zeiger et al., 1987; Table H1). α-Methylbenzyl alcohol, within a concentration range of 250-1,200 nl/ml, induced Tft resistance in mouse lymphoma L5178Y/TK cells in the absence of exogenous metabolic activation; this test was not performed with S9 (Table H2). The relative total growth of the cell cultures demonstrating a positive response was above 10%, indicating that excessive toxicity was not a complicating factor in this assay. In cytogenetic tests with CHO cells, α-methylbenzyl alcohol did not induce SCE or cell cycle delay when tested over a concentration range of 33-1,000 μg/ml with or without Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table H3). The chemical did, however, induce a significant increase in chromosomal aberrations in CHO cells, in the presence of S9, within a concentration range of 1,000-3,000 μg/ml (Table H4). Although the positive control cultures in Trial 1, +S9, failed to respond appropriately to cyclophosphamide treatment, the response observed with α-methylbenzyl alcohol at 3,000 μg/ml was still valid and was confirmed in Trial 2, +S9.

TABLE H1. MUTAGENICITY OF α-METHYLBENZYL 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	128 ± 4.9	107 ± 8.1	154 ± 10.9	110 ± 9.6	116 ± 4.9	102 ± 9.7
	33	114 ± 9.2	100 ± 3.8	138 ± 14.2	--	121 ± 7.7	--
	100	101 ± 2.3	95 ± 1.2	142 ± 4.2	102 ± 3.2	125 ± 1.5	98 ± 12.9
	333	131 ± 2.4	101 ± 9.5	134 ± 0.7	112 ± 7.8	126 ± 5.4	109 ± 8.3
	1,000	127 ± 11.1	120 ± 7.2	142 ± 2.3	114 ± 5.7	122 ± 10.1	106 ± 7.8
	2,166	129 ± 5.7	--	--	--	--	--
	2,500	--	(c) 113 ± 8.0	--	--	--	--
	3,333	--	--	(c) 140 ± 6.8	(c) 101 ± 3.6	(c) 97 ± 6.8	(c) 102 ± 7.5
	6,666	--	--	--	Toxic	--	(c) 66 ± 0.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		1,023 ± 60.4	1,238 ± 38.6	519 ± 14.0	902 ± 13.3	377 ± 7.7	648 ± 38.7
TA1535	0	16 ± 2.3	18 ± 1.8	12 ± 2.3	12 ± 0.7	9 ± 0.9	14 ± 2.0
	33	24 ± 4.4	25 ± 2.3	9 ± 3.5	--	10 ± 3.5	--
	100	24 ± 2.0	20 ± 1.5	12 ± 2.3	12 ± 3.3	11 ± 1.5	12 ± 1.0
	333	17 ± 1.3	30 ± 2.0	8 ± 0.3	13 ± 0.9	11 ± 2.7	10 ± 1.2
	1,000	23 ± 2.6	20 ± 2.6	10 ± 1.9	11 ± 1.7	11 ± 2.7	14 ± 0.7
	2,166	(c) 15 ± 0.9	--	--	--	--	--
	2,500	--	(c) 22 ± 4.4	--	--	--	--
	3,333	--	--	12 ± 1.2	(c) 10 ± 0.6	10 ± 1.2	(c) 12 ± 1.2
	6,666	--	--	--	Toxic	--	Toxic
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		826 ± 33.4	843 ± 9.3	75 ± 8.1	58 ± 6.1	38 ± 2.7	72 ± 6.3
TA1537	0	4 ± 0.9	4 ± 0.6	5 ± 1.2	3 ± 1.0	6 ± 1.5	5 ± 1.2
	33	5 ± 1.2	5 ± 1.2	8 ± 2.3	--	10 ± 1.7	--
	100	5 ± 0.3	4 ± 1.5	8 ± 1.2	5 ± 2.4	9 ± 2.3	5 ± 1.0
	333	4 ± 0.9	4 ± 1.7	5 ± 0.3	5 ± 0.6	9 ± 0.7	5 ± 0.3
	1,000	7 ± 1.2	6 ± 1.2	9 ± 1.8	5 ± 1.3	9 ± 1.2	5 ± 2.1
	2,166	5 ± 1.3	--	--	--	--	--
	2,500	--	4 ± 0.3	--	--	--	--
	3,333	--	--	9 ± 1.5	5 ± 1.7	7 ± 0.0	3 ± 0.0
	6,666	--	--	--	(c) 4 ± 0.7	--	(c) 3 ± 0.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		345 ± 49.4	156 ± 16.2	72 ± 4.7	82 ± 2.4	29 ± 4.3	46 ± 2.6
TA98	0	19 ± 1.9	12 ± 1.3	24 ± 2.9	20 ± 4.0	21 ± 2.6	18 ± 3.2
	33	14 ± 3.8	13 ± 1.2	19 ± 2.8	--	27 ± 0.7	--
	100	13 ± 1.9	10 ± 1.3	24 ± 3.2	25 ± 2.5	27 ± 2.1	19 ± 0.3
	333	17 ± 2.0	14 ± 2.6	33 ± 4.9	23 ± 1.5	22 ± 0.3	17 ± 1.5
	1,000	17 ± 1.5	12 ± 2.0	20 ± 2.8	18 ± 2.3	24 ± 5.8	15 ± 3.1
	2,166	12 ± 2.7	--	--	--	--	--
	2,500	--	14 ± 1.9	--	--	--	--
	3,333	--	--	24 ± 1.7	23 ± 0.9	26 ± 1.0	14 ± 0.9
	6,666	--	--	--	Toxic	--	Toxic
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		928 ± 15	1,163 ± 14.0	1,039 ± 66.6	426 ± 13.3	319 ± 10.4	268 ± 6.6

(a) Study performed at EG&G Mason Research Institute. The detailed protocol is presented in Haworth et al. (1983); the data are included in Zeiger et al. (1987). 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 H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE IN MOUSE L5178Y LYMPHOMA CELLS BY α-METHYLBENZYL ALCOHOL (a,b)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
-S9					
Trial 1					
Ethanol (d)		60.5 ± 2.0	100.0 ± 7.0	181.0 ± 24.6	100.3 ± 14.3
α-Methylbenzyl alcohol	62.5	57.7 ± 5.2	64.3 ± 12.3	221.0 ± 15.1	131.0 ± 19.5
	125	58.3 ± 6.6	74.0 ± 11.2	200.7 ± 31.9	117.7 ± 22.6
	250	61.3 ± 3.8	46.3 ± 4.6	296.0 ± 17.1	(e) 161.3 ± 2.9
	(f) 375	57.0 ± 2.0	17.5 ± 6.5	307.0 ± 70.0	(e) 181.5 ± 47.5
	(f) 500	45.0 ± 0.0	14.5 ± 3.5	317.5 ± 22.5	(e) 237.0 ± 18.0
	750	Lethal	--	--	--
Methyl methanesulfonate	5 µg/ml	33.7 ± 4.3	33.7 ± 5.8	614.7 ± 120.3	(e) 604.0 ± 42.3
Trial 2					
Ethanol (d)		108.3 ± 3.6	100.0 ± 8.9	71.5 ± 14.8	21.8 ± 4.2
α-Methylbenzyl alcohol	300	96.3 ± 6.0	54.7 ± 8.3	60.0 ± 15.9	21.3 ± 6.2
	(g) 400	89	58	76	29
	500	100.3 ± 1.5	74.3 ± 2.2	65.7 ± 4.9	22.0 ± 1.7
	600	83.3 ± 11.4	44.3 ± 9.6	48.0 ± 2.5	19.7 ± 1.5
	800	94.3 ± 3.5	41.0 ± 0.0	40.3 ± 4.7	14.3 ± 2.2
	1,000	96.0 ± 6.1	31.0 ± 8.3	102.3 ± 12.0	(e) 36.3 ± 6.1
Methyl methanesulfonate	5 µg/ml	87.7 ± 5.2	61.3 ± 8.4	331.0 ± 15.7	(e) 127.7 ± 13.9
Trial 3					
Ethanol (d)		82.8 ± 11.2	100.0 ± 19.2	94.3 ± 9.4	38.8 ± 2.6
α-Methylbenzyl alcohol	400	92.0 ± 6.6	129.0 ± 8.6	86.7 ± 2.0	31.7 ± 1.5
	500	77.7 ± 2.0	84.0 ± 13.9	89.3 ± 8.4	38.3 ± 2.9
	600	88.7 ± 4.1	78.3 ± 12.8	118.0 ± 12.2	44.0 ± 2.5
	800	74.0 ± 5.0	58.7 ± 9.8	109.7 ± 5.5	50.0 ± 3.6
	1,000	92.7 ± 7.1	37.3 ± 11.5	202.3 ± 33.2	(e) 72.3 ± 7.9
	(f) 1,200	90.5 ± 6.5	34.0 ± 9.0	227.5 ± 26.5	(e) 85.0 ± 16.0
	1,500	Lethal	--	--	--
Methyl methanesulfonate	5 µg/ml	63.3 ± 3.3	63.7 ± 4.9	566.3 ± 33.3	(e) 299.3 ± 1.3

(a) Study performed at Litton Bionetics, Inc. 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 triplicate, unless otherwise specified; the average of the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

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

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

(d) Data presented are for four tests.

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

(f) Data presented are for two tests; the dose in one test was lethal.

(g) Data presented are for one test.

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY α-METHYLBENZYL 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)--Summary: Negative								
Dimethyl sulfoxide		50	1,043	396	0.38	7.9	26.0	
α-Methylbenzyl alcohol	33.3	50	1,046	430	0.41	8.6	26.0	108.9
	100	50	1,042	390	0.37	7.8	26.0	98.7
	333.3	50	1,037	403	0.39	8.1	26.0	102.5
Mitomycin C	0.001	50	1,042	527	0.51	10.5	26.0	132.9
	0.01	5	104	176	1.69	35.2	26.0	445.6
+S9 (d)--Summary: Negative								
Dimethyl sulfoxide		50	1,045	410	0.39	8.2	26.0	
α-Methylbenzyl alcohol	100	50	1,042	402	0.39	8.0	26.0	97.6
	333.3	50	1,045	423	0.40	8.5	26.0	103.7
	1,000	50	1,042	373	0.36	7.5	26.0	91.5
Cyclophosphamide	0.4	50	1,047	719	0.69	14.4	26.0	175.6
	2	5	103	251	2.44	50.2	26.0	612.2

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

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY α-METHYLBENZYL ALCOHOL (a)

Trial 1					Trial 2				
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
−S9 (b)--Harvest time: 10.5 h					**−S9 (b)**--Harvest time: 10.5 h				
Dimethyl sulfoxide					Dimethyl sufoxide				
	100	6	0.06	4.0		100	5	0.05	3.0
α-Methylbenzyl alcohol					α-Methylbenzyl alcohol				
1,000	100	10	0.10	7.0	1,000	100	7	0.07	6.0
1,500	100	9	0.09	7.0	1,500	100	8	0.08	6.0
2,000	100	8	0.08	6.0	2,000	100	6	0.06	6.0
Summary: Negative					Summary: Negative				
Mitomycin C					Mitomycin C				
0.04	100	28	0.28	24.0	0.05	100	38	0.38	25.0
0.0625	25	34	1.36	80.0	0.08	25	32	1.28	64.0
+S9 (c)--Harvest time: 12.5 h					**+S9 (c)**--Harvest time: 12.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	3	0.03	3.0		100	8	0.08	5.0
α-Methylbenzyl alcohol					α-Methylbenzyl alcohol				
1,000	100	7	0.07	6.0	1,000	100	20	0.20	10.0
2,000	100	10	0.10	9.0	2,000	50	19	0.38	30.0
3,000	25	20	0.80	60.0	3,000	25	31	1.24	80.0
Summary: Weakly positive					Summary: Positive				
Cyclophosphamide					Cyclophosphamide				
7.5	100	6	0.06	(d)6.0	7.5	50	22	0.44	30.0
37.5	100	5	0.05	(d)5.0	37.5	25	24	0.96	52.0

(a) Study performed at Litton Bionetics, Inc.; Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Positive control failed. This does not invalidate the response observed at 3,000 µg/ml.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft (August 1988) of NTP Technical Report No. 369 for the 2-year studies of α-methylbenzyl alcohol in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance support contractors. The audit included review of:

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

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, except that some or all records for cage filter type and source, light-cycle duration, room air-change rate, and storage conditions for dose mixtures were not available at the Archives. Records documented that dose mixtures were prepared, analyzed, and administered according to protocols. Observation of clinical signs, including masses, were made and recorded consistently. Recalculation of approximately 10% of the group mean body weight values in the Technical Report showed 21/25 for rats and 22/24 for mice to be correct; differences ranged from 1.9% to 8.8%. External masses observed inlife correlated well with masses noted at necropsy for both rats and mice. The disposition code and date of death recorded at necropsy for each unscheduled-death animal (185 rats and 73 mice) had matching entries in the inlife records, except for the dates of death for 2 mice, which had no effect on survival values given in the Technical Report.

Individual animal identifiers (ear tags) were present and correct in the residual tissue bags for 62/69 rats and 59/70 mice examined. Review of the entire data trail for the 7 rats and 11 mice with less than complete and correct identifiers indicated that the integrity of their individual animal identity had been maintained, but the absence of ear tags had not been documented. A total of 5 untrimmed potential lesions were found in the wet tissues of 69 rats examined, whereas 9 were found in 70 mice examined; none involved target organs. Intestinal segments were not completely opened for 24/69 rats and 38/70 mice, and the stomach was partially opened in 13 rats; however, no potential lesions were evident by external examination. Gross observations made at necropsy were well correlated with microscopic diagnoses. Tissue blocks and slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables.

P values for the analysis of tumor incidence given in the Technical Report were the same as those in the final pathology tables in the study records.

Full details about these and other audit findings are presented in the audit reports that are on file at NIEHS. This summary describes the extent to which the data and factual information presented in the draft Technical Report for the 2-year gavage studies of α-methylbenzyl alcohol are supported by the records at the NTP Archives.

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