NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 250

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZYL ACETATE

(CAS NO. 140-11-4)

IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

Special Note: This Technical Report was peer reviewed in public session and approved by the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee in June 1982 and June 1983. Thereafter, the NTP adopted the policy that the experimental data and laboratory records from all NTP Toxicology and Carcinogenesis Studies not yet printed and distributed would be audited. [A summary of the data audit is presented in Appendix O.] Consequently, printing and distribution of this Technical Report have been delayed and the format differs from that of Technical Reports peer reviewed more recently. This final Technical Report supercedes all previous drafts of this report that have been distributed.

NTP TECHNICAL REPORT
ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BENZYL ACETATE (CAS NO. 140-11-4) IN F344/N RATS AND B6C3F$_1$ MICE (GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P. O. Box 12233
Research Triangle Park
North Carolina 27709

August 1986

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

NOTE TO THE READER

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

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

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

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

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

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

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

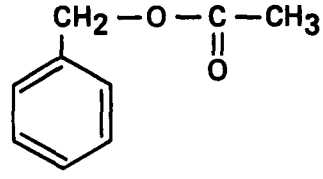
These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public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

TABLE OF CONTENTS

TABLES

FIGURES

APPENDIXES



BENZYL ACETATE

CAS NO. 140-11-4

$C_9H_{10}O_2$ Mol. Wt. 150.2

Synonyms: alpha-acetoxytoluene; benzyl ethanoate; acetic acid, benzyl ester

Melting Point: –51°C	Vapor Pressure: 1.99 mm Hg at 60°C
Boiling Point: 213°C	Density: 1.05
	Refractive Index: M_D^{25} = 1.4998

ABSTRACT

Toxicology and carcinogenesis studies of benzyl acetate (>99% pure) were conducted by administering benzyl acetate in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 0, 250, or 500 mg/kg body weight and to groups of 50 male and 50 female B6C3F$_1$ mice at doses of 0, 500, or 1,000 mg/kg once daily five days per week for 103 weeks. Dose selection for the 2-year study was based on mean body weight gain depression and decreased survival observed at higher doses in 13 week studies.

The absence of any observable adverse effect of benzyl acetate on the survival or mean body weight gains of the rats or mice in the 2-year studies suggests that both the rats and the mice of each sex could have tolerated higher doses. An infection in the genital tract was probably responsible for the deaths of 26/35 control, 14/32 low-dose, and 8/20 high-dose female mice before the end of the study.

Acinar-cell adenomas in the pancreas of male rats occurred with a positive trend ($P<0.01$), and the incidence in the high-dose group (37/49, 76%) was significantly ($P<0.01$) higher than in the vehicle controls (22/50, 44%). The incidence of these tumors in the low-dose group (27/50, 54%) was comparable to that in the gavage controls. Acinar-cell hyperplasia of the pancreas was observed in 37/50 control, 34/50 low-dose, and 36/49 high-dose male rats. No acinar-cell hyperplasia or adenoma of the pancreas was observed in female rats.

The incidence of retinopathy and cataracts in the high-dose male rats was increased compared with the controls (retinopathy: 1/50; 0/50; 20/50; cataracts: 0/50; 0/50; 13/50). Low-dose female rats had an increased incidence of retinopathy (18/50). Retinopathy and cataracts in rats have been associated with proximity to fluorescent light in this and previous studies.

Preputial gland neoplasms occurred with a positive trend ($P<0.05$) in male rats (cystadenocarcinoma: 0/50; 0/50; 3/50; all adenocarcinoma: 0/50; 1/50; 4/50; adenocarcinoma or carcinoma combined: 1/50; 1/50; 6/50). However, the incidence of all preputial gland tumors was not significantly elevated (2/50; 1/50; 6/50). For female rats the incidence of clitoral gland neoplasms was marginally increased (2/50; 0/50; 5/50).

Hepatocellular adenomas occurred in mice of each sex with statistically significant positive trends (males: 0/50; 5/49; 13/50; females: 0/50; 0/50; 6/50), and the incidences in the high-dose groups were greater than those in the controls (males: $P<0.001$; females: $P<0.05$). Heptocellular carcinomas were marginally elevated in dosed male and high-dose female mice (males: 10/50; 14/49; 12/50; females: 1/50; 0/50; 4/50).

Squamous cell papillomas or carcinomas of the forestomach (uncommon neoplasms) occurred with a positive trend ($P<0.05$) in male mice (4/49; 4/48; 11/49). The incidence of these tumors was also marginally ($P=0.054$) increased in the high-dose female mice (0/50; 0/50; 4/48). The incidences of these tumors in both the high-dose male and the high-dose female mice were considerably higher than the historical corn oil gavage control rates at this laboratory (males, 2/296, 0.7%; females, 2/297, 0.7%) and throughout the program (males, 14/1,070, 1.3%; females 3/1,073, 0.3%). Forestomach hyperplasia occurred at increased incidences in dosed mice of either sex (males: 1/49, 7/48, 22/49; females: 1/50, 6/50, 17/48). These neoplasms and hyperplasia of the forestomach were probably related to administration of benzyl acetate.

In a separate metabolism study, benzyl acetate was absorbed from the gastrointestinal tract of rats and mice, with approximately 90% of the administered dose recovered as various metabolites in the urine within 24 hr. The primary metabolite was hippuric acid, with minor amounts of a mercapturic acid, and one or more unidentified metabolites. This capacity for absorption, metabolism, and disposition was unaffected by the amount or number of doses administered.

Benzyl acetate was not mutagenic in strains TA100, TA98, TA135, or TA137 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced Sprague-Dawley rat or Syrian hamster S9 when tested according to the preincubation protocol. Benzyl acetate did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of Aroclor 1254-induced Sprague-Dawley rat liver S9. Benzyl acetate was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the presence, but not in the absence, of Aroclor 1254-induced Fisher 344 rat liver S9.

An audit was conducted on the experimental data and the draft technical report for these 2-year studies on benzyl acetate. Based on the results of this audit additional pathology examinations were conducted on all target organs in male rats and male and female mice. The Technical Report reflects these final pathology evaluations. The overall conclusions regarding the toxicology and carcinogenicity of benzyl acetate did not change as a result of this evaluation.

Under the conditions of these gavage studies, benzyl acetate increased the incidence of acinar-cell adenomas of the exocrine pancreas in male F344/N rats; the gavage vehicle may have been a contributing factor. There was no evidence of carcinogenicity* for female F344/N rats. For male and female B6C3F$_1$ mice there was some evidence of carcinogenicity in that benzyl acetate caused increased incidences of hepatocellular adenomas and squamous cell neoplasms of the forestomach.

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

CONTRIBUTORS

These studies were was conducted at Southern Research Institute under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The 2-year study in rats was begun in November, 1978. The 2-year study in mice was begun in August, 1978.

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

June, 1982

On June 16, 1982 the draft Technical Report on the toxicology and carcinogenesis studies of benzyl acetate underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Holland, a principal reviewer, agreed with the conclusions. He added that the evidence indicating the potential tumorigenicity of benzyl acetate was strengthened further by the increased incidence of preputial gland neoplasms (benign and malignant) in high-dose male rats. He commented on the probable diagnostic ambiguity between testicular hyperplasia and neoplasia, and recommended that the NTP develop criteria specifying what would be accepted as leydig cell neoplasia relative to hyperplasia.

As a second principal reviewer, Dr. Schwetz agreed with the overall conclusions of this study. He said that the papillomas and carcinomas of the forestomach occurred in both control and treated male mice, and the marginal increase in the high-dose group was likely associated with local irritation at the site of gavage. Importantly, little change was observed in the stomach of either sex or species. With regard to testicular tumors, he stated that if hyperplasia was included with tumors, there was no effect of benzyl acetate in the high-dose male rats. As a third principal reviewer, Dr. Elashoff agreed with the conclusions in the report.

Dr. L. Golberg, as a consultant for the Research Institute for Fragrance Materials, said the known metabolites of benzyl acetate were nonmutagenic and likely not carcinogenic per se; he speculated that the stomach tumors were due to a promotional effect or local formation of benzyl chloride. He also questioned certain of the statistical procedures. Dr. Breslow said the current statistical procedures resulted from an intensive evaluation by a group which included members of the Peer Review Panel.

Dr. Elashoff moved that the Technical Report be accepted subject to minor modifications, Dr. Highland seconded the motion and the report was approved unanimously by the Peer Review Panel.

January, 1983

On January 12, 1983, a letter was sent to all Peer Review Panel members who were present at the review held on 16 June 1982. The letter and attachments described changes proposed for the Technical Report because several untrimmed potential lesions were found in the pancreas of vehicle control male F344/N rats during a retrospective audit of the pathology materials.

June, 1983

On June 29, 1983, the draft Technical Report was again reviewed by the Peer Review Panel. Dr. Hook, Chairperson, reviewed the two previous actions by the Panel on the drafts of the Technical Report. Dr. B. Bernard, Flavor and Extract Manufacturers Association (FEMA), and Mr. N. Mantel and Dr. C. Weil, representing FEMA and the Fragrance Manufacturers Association (FMA), made presentations to the Panel contending that the NTP benzyl acetate studies were inadequate studies of carcinogenicity because of major qualitative or quantitative limitations. Their position was that: (1) in male F344/N rats, the use of corn oil gavage was a confounding variable that left the causation of pancreatic acinar cell adenomas unclear; (2) in female $B6C3F_1$ mice, intercurrent infection and other study factors resulted in excessive non-random mortality, greater than 50% in both control and low dose groups, thus prohibiting analysis of the possible association of benzyl acetate with the increased incidence of liver adenomas; and (3) in male $B6C3F_1$ mice, the incidence of liver adenomas in the vehicle control group was unusually small compared with historical corn oil gavage or untreated controls or with concurrent untreated controls, and the incidence of liver adenomas in the benzyl acetate dosed groups fell within the range of historical control values. Dr. Bernard recommended that the conclusions of the Technical Report be changed to reflect these considerations.

The two Panel members who served as principal reviewers of the benzyl acetate report in June 1982 responded: Dr. R. M. Elashoff (biostatistician) and Dr. J. M. Holland (pathologist). Dr. Elashoff said that to his knowledge there are no data available showing a synergism between corn oil and benzyl acetate in producing tumors. He stated that the apparent genetic inhomogeneity for the $B6C3F_1$ mice is more likely to lead to an increase in the false negative direction, not in the false positive rate. Dr. Elashoff had a number of comments on issues of experimental design and statistical analyses. He emphasized that the concurrent vehicle control group was always the most appropriate control group for any study, not the untreated controls (which were sacrificed at weeks 53 to 55, too early to provide meaningful data on tumor incidence) or historical controls. Further, if one considered the incidence of combined adenomas and carcinomas in male mice in this study and in historical controls receiving corn oil by gavage, there was considerable variability among groups. He said the high variability in the presence of inhomogeneity made it difficult to label any of the control groups as aberrant, and strongly favored the use of concurrent controls rather than historical controls for comparison with treated groups. With regard to female mice, although there was decreased survival, the statistical tests that adjust for decreased survival, life table and incidental tumor analyses, show significance. With respect to liver adenomas alone or adenomas and carcinomas combined, there were dose-response trends and vehicle control vs. high dose effects for both male and female mice. Dr. Elashoff felt that the consistency of the effect in both male and female mice supported the biological significance of the increased liver tumor incidence, and he stated that he approved of the conclusions in the current draft Technical Report.

Dr. Holland said he did not believe there were any substantive errors in the data that would influence interpretation. He thought the issue of the low liver tumor frequencies in the concurrent male vehicle control mice was indeed worthy of discussion and that this important topic had been addressed adequately by Dr. Elashoff. He suggested that use of confidence intervals with historical controls might allow the reader a better awareness of any degree of variability. He said the Technical Report should reflect the differences in interpretation raised by the FEMA/FMA positions, and the responses by the NTP to those interpretations. He concluded that the current draft report should be accepted in its present form.

Dr. Swenberg proposed using the new NTP categories of evidence (page 2), adopted at the same meeting. Based on the low incidences in male mouse vehicle controls and the general question of variability in male $B6C3F_1$ mouse liver tumors, he proposed that the evidence was equivocal for carcinogenicity in mice. Dr. Van Ryzin suggested the historic controls should also be used in analyzing the mouse data. Dr. Davis asked that increases in nonneoplastic effects in mice be discussed. Dr. Friess said the Panel needed to reach some consensus on a number of the issues raised including survival and health status in mice and the occurrence and interpretations of liver lesions; appropriateness of historical vs. concurrent vehicle controls; and statistical issues. Dr. Davis disagreed that consensus was required or even likely, given the uncertainties discussed. Dr. Scala noted three issues he considered most important: survival in mice, corn oil gavage as an influencing factor, and the complex of statistical considerations.

Dr. Hook asked for a motion to (1) accept the draft technical report as written, (2) modify the conclusions using the new categories, or (3) send the report back to NTP for further revisions. Dr. Swenberg moved that the conclusion be modified to reflect the new categories; he suggested that the evidence was equivocal for both the rat pancreatic tumors and the mouse liver lesions. Dr. Beliczky seconded the motion. Before asking for a Panel vote, Dr. Hook said the revised report should include discussion reflecting the divergence of opinions, an indication of the extent of the record reviewed and submissions by FEMA/FMA, and a definition of the new categories describing weight of evidence in the Note to the Reader section of this and all future Technical Reports.

Dr. Bernard reiterated several of the points made earlier by the FEMA/FMA consultants. He said one could not ignore the statistical differences seen in male mice between concurrent vehicle and historical vehicle controls that along with the incidence of liver adenomas in the concurrent untreated controls did not support the low rates in the concurrent vehicle control values. Thus, he said the evidence supported an equivocal finding. Dr. Friess interpreted the studies in mice as showing a marginal increase in neoplasms. "Marginal" needed to be emphasized to reflect the uncertainties in the data and the differing opinions on the conclusions. Dr. Huff, NTP, said that when liver adenomas and carcinomas are combined, the combination for male mice remains statistically significant, and for

female mice the evidence for carcinogenicity is strengthened. The rate for combined tumors in vehicle controls is not different from historic rates for combined tumors in male mice. Dr. Swenberg noted that there was no difference in rates of hepatocellular carcinomas in high dose male mice compared to historical control mice at the same laboratory. After further discussion, Dr. Hook requested a vote: the motion for "equivocal evidence of carcinogenicity" was voted on by the Panel and rejected by four affirmative and six negative votes.

Discussion then ensued that the mouse data supported some evidence of carcinogenicity. Dr. Elashoff supported this, noting the significantly increased incidence in both male and female mice for both adenomas and adenomas and carcinomas (combined) as well as a general dose-response effect when compared to vehicle controls. Dr. Slaga agreed. Dr. Davis moved that the conclusion be some evidence of carcinogenicity, with an addendum in the discussion of the reproductive-related lesions. Dr. Beliczky seconded the motion. There was discussion as to whether the untreated control group should be included since it was considered inappropriate to compare tumor incidences in one- and two-year-old control animals. A program decision had been made to terminate a number of untreated control groups. The fact that the untreated controls had liver tumors diagnosed at the one-year sacrifice served to further highlight the lower than usual rates in the concurrent vehicle control mice. The Panel agreed that the motion referred only to the findings in $B6C3F_1$ mice; the rat data were not at issue.

Dr. Hook asked that the conclusion to be voted on be read: "Under the conditions of these gavage studies, benzyl acetate caused an increased incidence of acinar-cell adenomas of the exocrine pancreas in male F344/N rats; the gavage vehicle may have been a contributing factor. There was no evidence of carcinogenicity for female F344/N rats. For male and female $B6C3F_1$ mice there was some evidence of carcinogenicity in that benzyl acetate caused increased incidences of hepatocellular adenomas." Dr. Swenberg pointed out that the conclusion in male mice was based on a comparison with concurrent vehicle controls. Dr. Hook said all the concerns as discussed would be added to the report.

The Technical Report on benzyl acetate with the conclusions as read was approved by eight affirmative votes. There were two negative votes (Dr. Scala and Dr. Swenberg).

November, 1984

On November 2, 1984 an update on the toxicology and carcinogenesis studies of benzyl acetate following a retrospective data audit was presented to the Peer Review Panel by Dr. J.E. Huff and Dr. K.M. Abdo of NTP. Dr. Huff noted that the NTP would report routinely to the Panel on chemicals for which a subsequent data audit or other studies on the chemical revealed some interesting findings. With respect to benzyl acetate there were two types of findings: one relating to NTP metabolism and genotoxicity studies, and the second concerning the key findings made and resolved during the audit. The Technical Report for benzyl acetate was approved by the Panel on June 29, 1983, prior to the decision that all studies would receive data audits before coming to the Panel for review. Dr. Huff reported that the new findings will be incorporated into a draft copy of the Technical Report and sent to Panel members plus former members involved in peer review of the report.

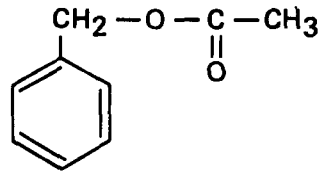
Dr. Abdo described a study of the metabolism and disposition in adult male F344 rats and $B6C3F_1$ mice of ring-labeled ^{14}C-benzyl acetate (BA) by the NIEHS/NTP Chemical Disposition section. The high dose used was the same as the high dose used in the two-year studies. Results from both groups indicated rapid and nearly complete absorption from the gastrointestinal tract, rapid excretion primarily in the urine, and no detectable tissue retention of BA-derived radioactivity. There was no dimunition of clearance upon repeated dosing for 14 days. Analyses of urine by high performance liquid chromatography (HPLC) show that hippuric acid accounted for over 90% of the urinary radioactivity with mercapturic acid and benzyl alcohol being other metabolites while no benzyl acetate was detected. There was no alteration in the pattern of chemical disposition after repeated dosing. Thus, there was no evidence to indicate any saturation of the mechanisms of absorption, metabolism, or excretion of benzyl acetate in either rats or mice over the dose range studied. [The results of this study are summarized in Appendix H.]

Second, Dr. Abdo reported on the NTP short term genetic toxicology findings. BA was not mutagenic in several strains of *Salmonella typhimurium* with or without metabolic activation and did not induce sister chromatid exchanges or chromosome aberrations in Chinese hamster ovary cells; BA was mutagenic in cultured mouse lymphoma cells in the presence but not in the absence of rat liver S9 extracts. [The results of this study are summarized in Appendix G.]

Third, Dr. Abdo reported on the findings from the data audit of the two-year studies of BA in rats and mice. He said the audit supported the results previously reported, and, further, confirmed the forestomach as a target organ for carcinogenicity in the mouse as noted in the amended conclusion. The results indicate that squamous cell papillomas or carcinomas and hyperplasia of the forestomach of mice of either sex were associated with BA administration. He emphasized that the information presented did not change the level of evidence for the carcinogenic effect of BA. [A summary of the data audit findings is in Appendix O.]

I. INTRODUCTION

I. INTRODUCTION



BENZYL ACETATE

CAS NO. 140-11-4

$C_9H_{10}O_2$ Mol. Wt. 150.2

Synonyms: alpha-acetoxytoluene; benzyl ethanoate; acetic acid, benzyl ester

Melting Point: –51°C
Boiling Point: 213°C
Vapor Pressure: 1.99 mm Hg at 60°C
Density: 1.05
Refractive Index: M_D^{25} = 1.4998

Benzyl acetate, a water-white liquid with a pear-like odor, is a natural constituent of several essential oils and flower absolutes extracted from jasmine, hyacinth, gardenia, tuberose, ylang-ylang, cananga, and neroli. Commercial benzyl acetate, a liquid prepared synthetically from benzyl chloride, acetic acid, and triethylamine (Fenaroli, 1971; Merck, 1976), is used primarily as a component of perfumes for soaps and as a flavoring ingredient (Kirk-Othmer, 1967; Balsam and Sagarin, 1972). This compound is practically insoluble in water but is miscible in alcohol and ether and soluble in benzene and chloroform.

The Joint FAO/WHO Expert Committee on Food Additives approved an acceptable daily intake (expressed as total benzoic acid) of 0-5 mg/kg body weight for humans (Opdyke, 1973), and the U.S. Food and Drug Administration has approved benzyl acetate for use as a flavoring ingredient (USCFR, 1979). Benzyl acetate may be found in foods at the following approximate concentrations: chewing gum, 760 ppm; puddings and gelatins, 23 ppm; candy, 34 ppm; baked goods, 22 ppm; ice cream, 14 ppm; and non-alcoholic beverages, 7.8 ppm (Fenaroli, 1971).

Benzyl acetate is also used as a solvent for cellulose acetate and cellulose nitrate (Merck, 1976). Approximately 1.4 million pounds of benzyl acetate were produced in the United States in 1980 (USITC, 1981).

An oral LD50 value of 2.49 g/kg body weight has been reported for male and female Osborne-Mendel rats (Jenner et al., 1964). In rats, benzyl acetate is hydrolyzed to benzyl alcohol, which is oxidized to benzoic acid and excreted as hippuric acid and benzyl mercapturic acid (Clapp and Young, 1970; Snapper et al., 1925). Urine flow in dogs and rabbits increased approximately 180% two hours after they received an intraperitoneal injection of 0.4 ml/kg body weight (Gruber, 1924).

In a chemical disposition study conducted by the NTP, male Fischer 344 rats and male B6C3F$_1$ mice were shown to efficiently absorb and rapidly metabolize and excrete orally administered benzyl acetate (Appendix H). The doses used in this study were 5, 50, or 500 mg/kg for rats and 10, 100, or 1,000 mg/kg for mice in single-dose corn oil gavage administrations and 500 mg/kg for rats and 1,000 mg/kg for mice daily five times per week for two weeks, also administered by gavage in corn oil. Most (90%) of the benzyl acetate-derived radioactivity was recovered in the urine and none was detected in the liver, blood, muscle, adipose tissue, skin, lung, kidney, or stomach of treated rats or mice. The major metabolite isolated in the urine was hippuric acid (94.6% - 99.3% of the dose). Other metabolites found were mercapturic acid and benzyl alcohol. Benzyl acetate was not detected in the urine of treated animals. Neither the size of the dose nor the frequency of dosing had any

effect on the absorption, metabolism, or excretion of this compound. There was no evidence to indicate any saturation of this metabolizing capacity in either species over the range of doses studied.

Benzyl acetate produces respiratory tract irritation and narcotic effects in humans, and continued exposure to benzyl acetate at an ambient concentration of 50 ppm results in kidney damage (Handbook of Organic Industrial Solvents, 1961; Opdyke, 1973). When ingested, benzyl acetate can cause general intestinal irritation (Clayton and Clayton, 1981).

Benzyl acetate gave negative results in an assay for differential killing of repair-proficient and -deficient strains of *Bacillus subtilus* H17 and M45 (Oda et al., 1978), and it was not mutagenic in strains TA1535, TA1537, TA98, or TA100 of Salmonella in the presence or absence of Aroclor 1254-induced rat liver S9 (Florin et al., 1980). In tests performed by the NTP, neither benzyl acetate (Appendix G) nor benzyl alcohol (Mortelmans et al., 1985) was mutagenic in Salmonella in the presence or absence of Aroclor 1254-induced Sprague-Dawley rat or Syrian hamster liver S9. In cultured Chinese hamster ovary cells, benzyl acetate did not induce sister-chromatid exchanges or chromosomal aberrations (Appendix G). Benzyl acetate was mutagenic in the L5178Y/TK^{+}/$^{-}$ mouse lymphoma assay in the presence, but not in the absence, of Aroclor 1254-induced rat liver S9 (Appendix G). Benzyl acetate did not induce unscheduled DNA synthesis in Fischer 344 rat hepatocytes following in vivo and in vitro treatment (Mirsalis, 1983).

The NTP studied benzyl acetate because of widespread consumer exposure to products containing this compound and because no long-term carcinogenesis studies had been performed. Although human exposure to benzyl acetate is primarily in food, it was administered by gavage because of its volatility and its reactivity with moisture present in feed.

II. MATERIALS AND METHODS

CHEMICAL ANALYSES

DOSAGE PREPARATION

SINGLE-DOSE STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Test Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS: CHEMICAL ANALYSES

CHEMICAL ANALYSES

Food-grade benzyl acetate was obtained from the Chemical Division of UOP, Inc. (Rutherford, NJ) in three batches. Lot No. 9640 was used for the short-term studies; Lot No. 4821 was used for the first 18 months of the 2-year study; and Lot No. 12952 was used for the final 6 months of the 2-year study. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO); methods used and results obtained are presented in Appendix I.

When benzyl acetate was hydrolyzed and then back titrated, the ester values found were 96.0% (Lot 9640), 99.1% (Lot 4821), and 101.3% (Lot 12952). Results of elemental analysis for carbon and hydrogen in all lots agreed with the theoretical values.

When all three lots were analyzed by vapor-phase chromatography, the impurities in all constituted less than 1% of the major peak. The only difference was in the number of impurities found in each lot: four in Lot 9640, six in Lot 4821, and three in Lot 12952. None of the impurities was characterized initially. The infrared, ultraviolet, and nuclear magnetic resonance spectra of all three batches were consistent with the literature spectra.

The two lots (No. 4821 and 12952) of benzyl acetate used in the 2-year studies met the Food Chemical Codex (FCC) specification. The ester values met the minimum FCC requirement of 98.0% but were greater than the generally specified maximum of 100.5% (Appendix J). Benzyl alcohol was identified as an impurity in both lots. Chlorine contents as measured by the combustion and microcoulometric titration method were 0.005% for Lot No. 4821 and 0.003% for Lot No. 12952 (Appendix J).

Benzyl acetate was stored at 5° C throughout the study. Periodic reanalysis of benzyl acetate at Southern Research Institute by infrared and gas-liquid chromatography indicated no changes in the composition of any of the lots of the bulk chemical during their time of use.

The chemicals used in these studies of benzyl acetate were analyzed by the Midwest Research Institute. Reanalysis of the bulk chemical and analysis of chemical/vehicle mixtures were performed at Southern Research Institute.

DOSAGE PREPARATION

Doses were prepared on a weight-to-volume basis by pipetting the appropriate amount of benzyl acetate into a vessel and adding enough corn oil to give the desired concentration. Solutions were mixed until they were visually homogeneous. Rats received 5 ml/kg and mice 10 ml/kg body weight. Benzyl acetate/corn oil mixtures were analyzed at Midwest Research Institute and found to be stable at room temperature for at least 7 days (Appendix K). Once prepared, benzyl acetate/corn oil mixtures were stored at 5° C for no longer than 11 days.

Samples of benzyl acetate in corn oil were selected at random and analyzed periodically at Southern Research Institute (Appendix L). Results of these analyses and of referee analyses at Midwest Research Institute indicated that benzyl acetate/corn oil mixtures were properly formulated.

SINGLE-DOSE STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and observed for 7 days before the test began. Animals were approximately 5 weeks old when placed on study.

Groups of five rats and mice of each sex were administered a single dose of benzyl acetate (250,

500, 1,000, 2,000, or 4,000 mg/kg body weight) in corn oil by gavage. No controls were used. All animals were examined twice daily for clinical signs and mortality during the 15-day observation period.

Animals were housed five per cage and received water and feed *ad libitum* during the observation period. Details of animal maintenance are presented in Table 1. Necropsies were not performed.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 12 days. Animals were approximately 6 weeks old when placed on study.

Groups of five rats of each sex were administered 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg benzyl acetate in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg benzyl acetate in corn oil by gavage for 14 consecutive days.

Animals were housed five per cage and received water and feed *ad libitum*. Details of animal maintenance are presented in Table 1. Rats and mice were observed daily for mortality and were weighed weekly. On day 16, surviving animals were killed and necropsies were performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of benzyl acetate and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries, observed for 13 days, and assigned by species and sex to cages according to a table of random numbers. The cages were then assigned to dosed and control groups according to another table of random numbers.

Rats and mice were housed five per cage in polycarbonate cages covered with spun-bonded polyester filters (Table 1). Racks and filters were replaced every 2 weeks. Cages and bedding were replaced twice per week. Water, via an automatic watering system, and Wayne Lab Blox® were available *ad libitum*.

Groups of 10 rats of each sex and groups of 10 male mice were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg benzyl acetate in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 female mice were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg on the same schedule.

Animals were checked for mortality and signs of morbidity twice daily. Those animals that were judged moribund were killed and necropsied. Each animal was given a clinical examination weekly, including palpation for tissue masses or swelling. Individual body weight data were collected weekly.

On days 92-96, survivors were killed with carbon dioxide. Necropsies were performed on animals that survived to the end of the study and on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. The following specimens were examined microscopically for controls, for the highest dosage group with at least 60% survivors at the time of the group kill, and for all animals that died before the survivors of the group were killed: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
Experimental Design				
Size of Test Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Male and female rats: 250, 500, 1,000, 2,000, or 4,000 mg/kg body weight in corn oil	Male and female rats: 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg body weight in corn oil	Male and female rats and male mice: 0, 62.5, 125, 250, 500, or 1,000 mg/kg body weight in in corn oil	Male and female rats: 0, 250, or 500 mg/kg body weight in corn oil
	Male and female mice: 250, 500, 1,000, 2,000, or 4,000 mg/kg body weight in corn oil	Male and female mice: 0, 125, 250, 500, 1,000, or 2,000 mg/kg body weight in corn oil	Female mice: 0, 125, 250, 500, 1,000, or 2,000 mg/kg body weight in corn oil	Male and female mice: 0, 500, or 1,000 mg/kg body weight in corn oil
Duration of Dosing	Single dose	14 consecutive days	13 weeks (5 days/week)	103 weeks (5 days/week)
Type and Frequency of Observation	Observed twice daily for mortality and clinical signs for 14 days.	Observed daily for mortality and clinical signs.	Observed twice daily for mortality and morbidity; clinical examinations weekly	Observed twice daily for mortality and morbidity. Clinical observations recorded at each weighing period: weekly for first 13 weeks, monthly until week 91, and then every 2 weeks.
Necropsy and Histologic Examination	None	Necropsies performed on all animals	Necrospies performed on all animals; following tissues examined histologically in control and highest-dose groups with 60% survivors: brain, pituitary, salivary glands, esophagus, mandibular lymph node, thymus,	All animals necropsied. All animals examined histologically; tissues examined: gross lesions, brain, pituitary, thymus, spleen, thyroid, parathyroid, lung, and bronchi, trachea,

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
			spleen, heart, thyroid, parathyroid, trachea, lungs and bronchi, stomach, liver, large and small intestines, pancreas, mesenteric lymph node, testicles or ovaries, prostate or uterus, seminal vesicles, mammary gland, skin, bone, bone marrow, thigh muscle, kidneys, urinary bladder, and adrenal glands, gross lesions, tissue masses, gallbladder (mice), nasal cavity, and spinal cord.	heart, esophagus, stomach (pylorus and fundus), duodenum, jejunum, ileum, large intestine, pancreas, adrenal, kidney, liver, gall-bladder (mice), skin, mammary gland, urinary bladder, prostate seminal vesicles testes or uterus ovaries, femur with marrow, abnormal lymph nodes, salivary, gland, thigh muscle, sciatic nerve, costo-chrondral junction, larynx, mesenteric lymph nodes, nasal cavity, and spinal cord.
Animals and Animal Maintenance				
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
Animal Source	Frederick Cancer Research Center Frederick, MD	Harlan Industries Indianapolis, IN	Harlan Industries Indianapolis, IN	Charles River Breeding Laboratories, Portage, MI
Time Held Before of Test	1 week	2 weeks	2 weeks	Rats: 3 weeks Mice: 2 weeks
Age When Placed on Study	5 weeks	6 weeks	6 weeks	Rats: 7 weeks Mice: 8 weeks

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
Age When Killed	7 weeks	8 weeks	19 weeks	Rats: 111-114 weeks Mice: 112-114 weeks
Method of Animal Distribution	Animals assigned by species and sex to cages according to a table of random numbers. Then cages assigned to control and test groups according to another table of random numbers.	Same as single-dose study	Same as single-dose study	Same as single-dose study
Feed	Wayne Lab-Blox® Allied Mills, Inc. Chicago, IL	Same as single-dose study	Same as single-dose study	Same as single-dose study
Bedding	Beta-Chips® heat treated hardwood chips, Northeastern Products Corp., Warrensburg, NY	Same as single-dose study	Same as single-dose study	Beta-Chips® or sawdust, P.W.I., Inc. Lowville, NY Changed twice weekly
Water	Tap water supplied through automatic watering system, Edstrom Automatic, Waterford, WI	Same as single-dose study	Same as single-dose study	Same as single-dose study
Cages	Polycarbonate, Lab Products Inc., Garfield, NJ	Same as single-dose study	Same as single-dose study	Same as single-dose study
Cage Filters	Spun-bonded polyester filters, Snow Filtration, Cincinnati, OH	Same as single-dose study	Same as single-dose study	Same as single-dose study

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)

	Single-Dose Study	Fourteen-Day Study	Thirteen-Week Study	Two-Year Study
Animals per cage	Rats: five Mice: five	Rats: five Mice: five	Rats: five Mice: five	Rats: five Mice: five
Animal Room Environment	15 room air changes/hr; 21°-23° C; 40%-60% relative humidity	Same as single-dose study	Same as single-dose study	15 room air changes/hr; 21°-24°C; 30%-60% relative humidity; 12 hrs of fluorescent light per day
Other Chemicals on Test in Same Room	None	None	None	None
Chemical/Vehicle				
Preparation	Benzyl acetate was dissolved in Mazola® corn oil	Same as single-dose study	Same as single-dose study	Same as single-dose study
Maximum Storage Time		1 week	1 week	11 days
Storage Conditions		21°-23°C	21°-23°C	5°C in amber serum bottles

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 250, or 500 mg/kg benzyl acetate in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex received 0, 500, or 1,000 mg/kg on the same schedule. Additional groups of 50 rats and 50 mice of each sex were included at the start of the two-year studies to serve as untreated controls. These controls were sacrificed early in the study (weeks 42-44 for rats and weeks 53-55 for mice) as a result of a programwide decision that vehicle controls are more appropriate than untreated controls for interpreting the results of gavage studies. These data are not given in this report because they were not considered directly relevant to the evaluation of the two-year findings.

Source and Specifications of Test Animals

Four-week-old male and female F344/N rats and 6-week-old $B6C3F_1$ mice were obtained from the Charles River Breeding Laboratories. Rats were observed for 3 weeks and mice for 2 weeks. Animals were assigned by species and sex to cages according to a table of random numbers. Cages were then assigned to dosed and control groups according to another table of random numbers.

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

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

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

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages (Table 1). No other chemicals were being tested in the same room. Cages and bedding were replaced twice per week. Tap water (via an automatic watering system) and feed were available *ad libitum*.

The temperature in the animal rooms was 21°-24°C and the humidity was 30%-60%. Fifteen changes of room air per hour were provided. Fluorescent lighting provided illumination 12 hours per day.

Animal disease condition at the laboratory was monitored by the use of sentinel rats and mice. Plasma samples were obtained from these animals (5 per sex and species) at 6, 12, and 18 months and from vehicle control animals at 24 months. These samples were assayed for the various viral serology titers and the results are presented in Appendix N.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of morbidity or mortality. Clinical signs were recorded monthly. Body weights by cage were recorded every week for the first 13 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the study were killed with carbon dioxide and necropsied.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following were examined microscopically: tissue masses, abnormal lymph nodes,skin, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart,

thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

Necropsies were performed on all animals found dead and on those killed at the end of the study, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

The pathology report and selected slides were evaluated by the NTP Pathology Working Group as described by Maronpot and Boorman (1983). The classification of proliferative lesions was done according to the criteria of Boorman and Eustis (1984). The diagnoses represent a consensus of contracting pathologists and the NTP Pathology Working Group.

Statistical Methods

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

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's method for testing for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence Rates: The incidence of neoplastic or nonneoplastic lesions has been 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 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 necropsies were performed.

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

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

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

Incidental Tumor Analyses—The second method of analyses 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: 0-52 weeks, 53-78 weeks, 79-92 weeks, week 93 to the week before the terminal kill period, and the terminal kill period. The denominators of these proportions were the number of animals on which necropsies were actually performed during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result. (See Peto et al., 1980, for the computational details of both methods.)

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

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

III. RESULTS

RATS

SINGLE-DOSE STUDY

FOURTEEN-DAY STUDY

THIRTEEN-WEEK STUDY

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-DOSE STUDY

FOURTEEN-DAY STUDY

THIRTEEN-WEEK STUDY

TWO-YEAR STUDY

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

SINGLE-DOSE STUDY

All animals that received benzyl acetate at 4,000 mg/kg body weight were inactive within 2 hours after dosing, and 4/5 males and 2/5 females in these groups died (all on day 2). No other compound-related clinical signs were observed.

FOURTEEN-DAY STUDY

All rats that received 4,000 mg/kg body weight were dead by the afternoon of day 2, and all rats that received 2,000 mg/kg were dead by the afternoon of day 5. No other rats died. Final mean body weights of both sexes of dosed rats were comparable to control animals (Table 2). The cecum was redder than normal in 3/5 males and 3/5 females that received 4,000 mg/kg.

Based on the mortality observed at the two highest dose levels, doses of 62.5, 125, 250, 500, and 1,000 mg/kg were selected for both sexes of rats in the 13-week study.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED BENZYL ACETATE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)*	Mean Body Weights (grams) Initial	Final	Change *(b)*	Final Weight Relative to Controls (percent)
Male					
0	5/5	123.8 ± 4.7	181.6 ± 9.4	+ 57.8 ± 4.9	
250	5/5	127.4 ± 2.7	180.2 ± 3.9	+ 52.8 ± 2.1	99.2
500	5/5	124.6 ± 7.5	174.6 ± 12.1	+ 50.0 ± 5.6	96.1
1,000	5/5	124.4 ± 6.0	173.2 ± 9.6	+ 48.8 ± 4.0	95.4
2,000	0/5 *(c)*	*(d)*	*(d)*	*(d)*	
4,000	0/5 *(e)*	*(d)*	*(d)*	*(d)*	
Female					
0	5/5	104.8 ± 1.5	128.0 ± 2.0	+ 23.2 ± 1.2	
250	5/5	103.0 ± 3.6	125.2 ± 6.1	+ 22.2 ± 2.7	97.8
500	5/5	106.0 ± 2.9	127.4 ± 2.7	+ 21.4 ± 1.5	99.5
1,000	5/5	106.4 ± 3.7	125.0 ± 5.0	+ 18.6 ± 1.3	97.7
2,000	0/5 *(c)*	*(d)*	*(d)*	*(d)*	
4,000	0/5 *(e)*	*(d)*	*(d)*	*(d)*	

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the group ± standard error of the mean.
(c) All died by day 5.
(d) No data are presented due to the 100% mortality in this group.
(e) All died by day 2.

III. RESULTS: RATS

THIRTEEN-WEEK STUDY

Two of ten males and 1/10 females that received 1,000 mg/kg died on day 86. No other animals died during the study. Final mean body weight in male rats receiving 1,000 mg/kg was about 12% lower than the control group (Table 3).

The only clinical signs attributed to compound administration were observed in male and female rats receiving 1,000 mg/kg and in females receiving 500 mg/kg. These signs included trembling, ataxia, and sluggishness. Thickened stomach walls were observed in 2/9 males and 4/10 females receiving 1,000 mg/kg. No compound-related histopathologic effects were observed.

Doses of benzyl acetate selected for rats on the 2-year study were 250 or 500 mg/kg body weight in corn oil by gavage.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS ADMINISTERED BENZYL ACETATE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)
		Initial	Final	Change *(b)*	
Male					
0	10/10	119.9 ± 4.5	328.3 ± 11.2	+ 208.4 ± 7.6	
62.5	10/10	117.0 ± 3.5	329.7 ± 10.3	+ 212.7 ± 8.5	100.4
125	10/10	127.1 ± 4.3	334.6 ± 12.0	+ 207.5 ± 9.1	101.9
250	10/10	124.6 ± 4.4	336.3 ± 7.6	+ 211.7 ± 6.4	102.4
500	10/10	116.6 ± 4.2	336.8 ± 6.5	+ 220.2 ± 5.1	102.6
1,000	8/10 *(c)*	123.3 ± 4.7	287.6 ± 8.7	+ 164.3 ± 6.2	87.6
Female					
0	10/10	96.7 ± 4.2	180.1 ± 8.2	+ 83.4 ± 5.2	
62.5	10/10	95.7 ± 3.2	188.3 ± 6.1	+ 92.6 ± 5.1	104.6
125	10/10	94.3 ± 1.9	179.9 ± 5.2	+ 85.6 ± 3.7	99.9
250	10/10	96.0 ± 3.4	183.2 ± 4.4	+ 87.2 ± 3.1	101.7
500	10/10	103.5 ± 4.4	198.1 ± 6.0	+ 94.6 ± 3.2	110.0
1,000	9/10 *(c)*	84.9 ± 3.0	170.4 ± 5.7	+ 85.5 ± 3.3	94.6

(a) Number surviving/number intially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the group ± standard error of the mean.
(c) Deaths occurred on day 86.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control male rats were comparable throughout most of the study (Table 4 and Figure 1). After week 20, mean body weights of high-dose female rats were slightly greater than those of controls.

Survival

Estimates of the probabilities of survival of male and female rats administered benzyl acetate by gavage at the doses of these studies, together with those of the control groups, are shown by the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups of either sex of rats (Table 5). In male rats, 38/50 (76%) of the controls, 46/50 (92%) of the low-dose group, and 40/50 (80%) of the high-dose group lived to the termination period of the study at 104-106 weeks. In female rats, 40/50 (80%) of the controls, 36/50 (72%) of the low-dose group, and 36/50 (72%) of the high-dose group lived to the termination period of the study at 104-106 weeks. Included in the survival data are one control male, one low-dose male, one control female, and one low-dose female rat that died during the termination period of the study. For statistical purposes, these animals are considered to have been killed at the end of the study.

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male rat and female rat studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2. Appendix E, Tables E1 and E2 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Pancreas: Acinar-cell hyperplasia was observed in all groups of male rats (Table 6). While the total number of rats with hyperplasia was fairly constant across dose groups, the hyperplastic lesions were more frequently multiple in the treated animals (Table 6). Acinar-cell hyperplasia can be recognized as a focal area that is more eosinophilic and stains more intensely than the adjacent pancreas. Hyperplastic lesions have cytological features similar to adenomas, such as variation in cell size, nuclear pleomorphism, and increased mitotic activity. However, lesions diagnosed as hyperplasias are smaller than adenomas, show little or no compression, and often appear contiguous with the adjacent unaffected parenchyma.

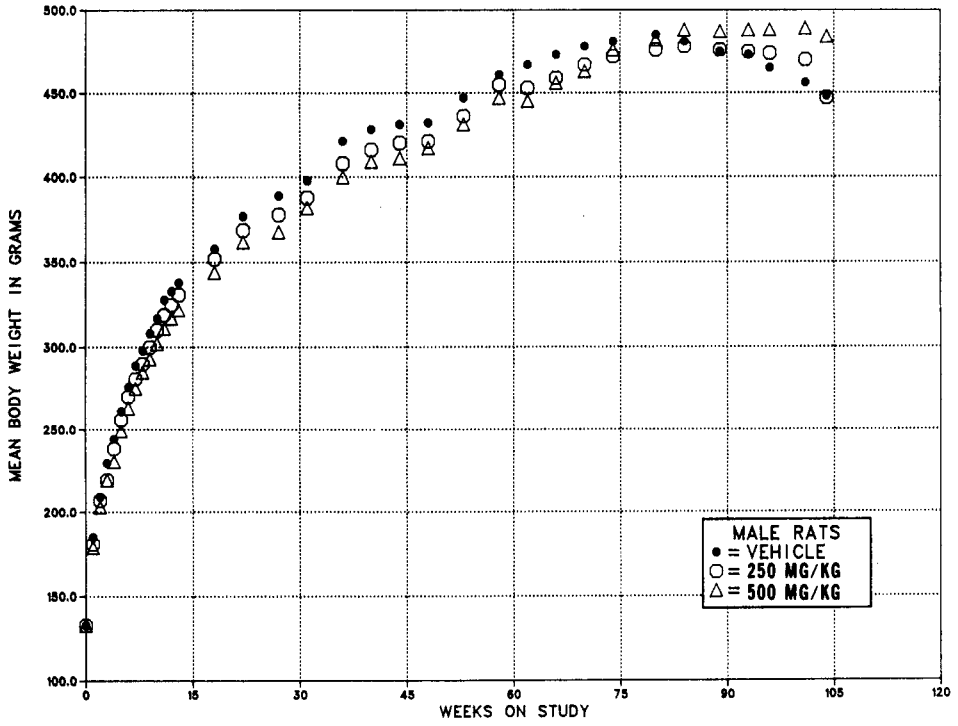
Acinar-cell adenomas in male rats occurred with a statistically significant ($P<0.01$) positive trend (Table 6). Results of the pairwise comparison with the controls were significant ($P<0.01$) for the high-dose group. The lesion was more often multiple in the treated animals. This tumor was not observed in any female rats.

The pancreatic adenomas were usually observed grossly and were characterized by variable degrees of peripheral compression. The cells in these lesions contained zymogen granules and were arranged like normal acinar cells, except that there was a lack of islet cells. Cells in the pancreatic lesions had slightly larger nuclei and the mitotic index was increased. Because of the increased mitotic activity and mild compression of adjacent tissues that caused a distinct line of demarcation, the pancreatic lesions were classified as acinar-cell adenomas.

Subcutaneous Tissue: The incidence of low-dose male rats with subcutaneous fibromas was significantly ($P<0.05$) higher than that of controls. Trend test results and comparisons between high-dose group and controls were not significant. The incidences of this tumor in male rats were: control, 3/50, 6%; low-dose, 11/50, 22%; high-dose, 5/50, 10%.

TABLE 4. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ACETATE

Weeks on Study	Control		250 mg/kg			500 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	133	50	133	100	50	133	100	50
1	185	50	181	98	50	179	97	50
2	209	50	207	99	50	203	97	50
3	229	50	219	96	50	219	96	50
4	244	50	238	98	50	230	94	50
5	261	50	256	98	50	249	95	50
6	276	50	270	98	50	263	95	50
7	289	50	281	97	50	275	95	50
8	298	50	290	97	50	285	96	50
9	308	50	300	97	50	293	95	50
10	317	50	310	98	50	302	95	50
11	328	50	319	97	50	311	95	50
12	333	50	325	98	50	317	95	50
13	338	50	331	98	50	322	95	50
18	358	50	352	98	50	344	96	50
22	377	50	369	98	50	362	96	50
27	389	50	378	97	50	368	95	50
31	398	50	388	97	50	382	96	50
36	421	50	408	97	50	400	95	50
40	428	50	416	97	50	409	96	50
44	431	50	420	97	50	411	95	50
48	432	50	421	97	50	417	97	50
53	447	50	436	98	50	431	96	50
58	461	50	455	99	50	447	97	50
62	467	50	453	97	50	445	95	49
66	473	50	459	97	50	456	96	49
70	478	50	467	98	50	463	97	49
74	481	50	472	98	50	476	99	49
80	485	49	476	98	50	482	99	46
84	481	48	478	99	48	488	101	46
89	475	46	476	100	48	487	103	45
93	473	41	475	100	47	488	103	45
96	465	41	474	102	47	488	105	44
101	456	40	470	103	47	489	107	43
104	448	38	447	100	46	484	108	40
FEMALE								
0	106	50	107	101	50	107	101	50
1	129	50	129	100	50	129	100	50
2	139	50	137	99	50	139	100	50
3	145	50	144	99	50	144	99	50
4	154	50	152	99	50	151	98	50
5	160	50	160	100	50	162	101	50
6	165	50	165	100	50	166	101	50
7	171	50	171	100	50	172	101	49
8	175	50	175	100	50	176	101	49
9	178	50	177	99	50	178	100	49
10	181	50	181	100	50	182	101	49
11	185	50	183	99	50	186	101	49
12	188	50	186	99	50	186	99	49
13	188	50	187	99	50	190	101	49
18	194	50	194	100	50	197	102	49
22	199	50	201	101	50	204	103	49
27	203	50	204	100	50	208	102	49
31	208	50	206	99	50	213	102	49
36	215	50	216	100	50	224	104	49
40	220	50	217	99	50	225	102	49
44	225	50	222	99	50	229	102	49
48	224	50	225	100	50	233	104	49
53	229	50	234	102	50	239	104	49
58	238	50	243	102	50	249	105	49
62	243	50	244	100	50	245	101	49
66	249	50	251	101	50	257	103	49
70	258	49	261	101	50	269	104	49
74	264	49	268	102	48	277	105	49
80	273	48	275	101	47	289	106	47
84	275	48	278	101	44	297	108	47
89	276	48	280	101	43	293	106	43
93	279	46	282	101	42	295	106	43
96	278	46	285	103	39	294	106	42
101	280	42	282	101	38	300	107	39
104	279	40	282	101	36	297	106	36



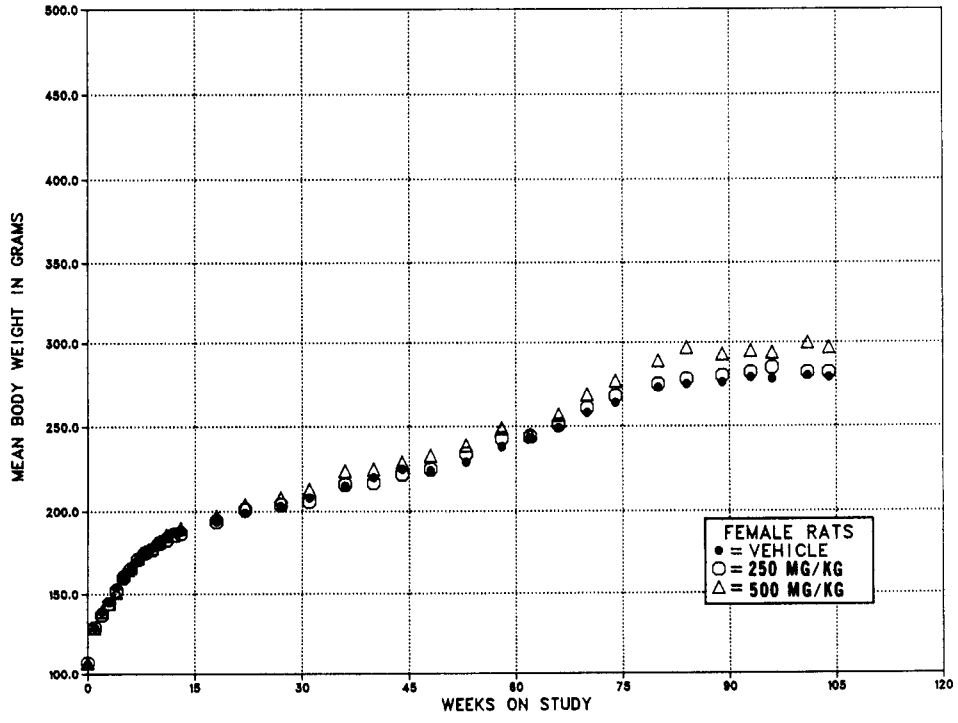
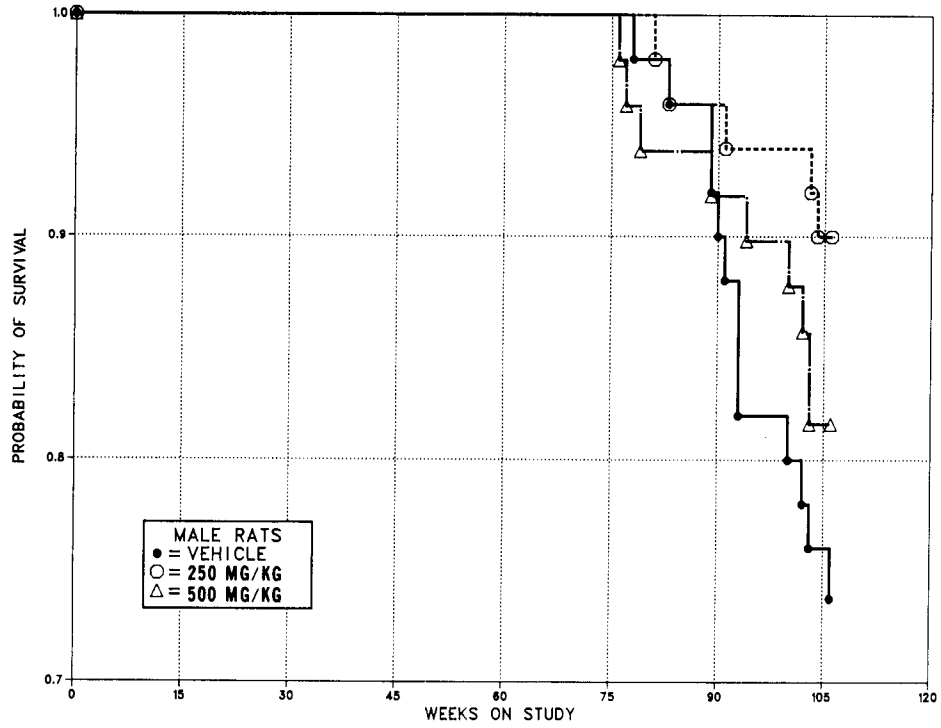


Figure 1. Growth Curves for Rats Administered Benzyl Acetate in Corn Oil by Gavage



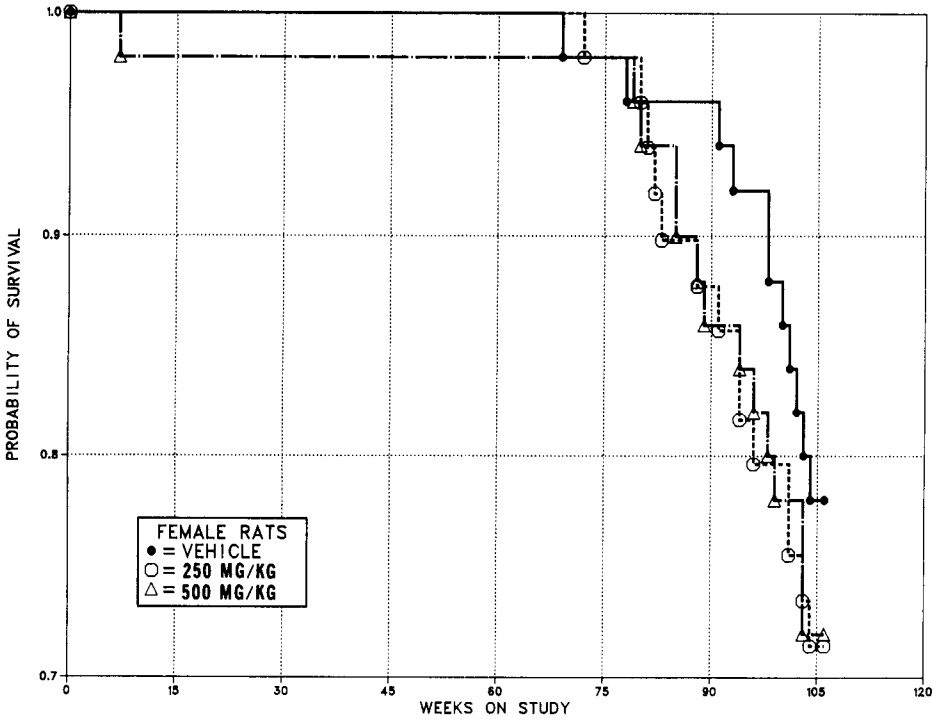


Figure 2. Kaplan-Meier Survival Curves for Rats Administered Benzyl Acetate in Corn Oil by Gavage

TABLE 5. SURVIVAL OF F344/N RATS IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ACETATE

	Vehicle Control	250 mg/kg	500 mg/kg
Male *(a)*			
Animals Initially in Study	50	50	50
Natural Death or Moribund Sacrifice	12	4	9
Accidental Death or Missing	0	0	1
Scheduled or Terminal Sacrifice	38	46	40
Survival P Values *(b)*	0.522	0.058	0.638
Female *(a)*			
Animals Initially in Study	50	50	50
Natural Death or Moribund Sacrifice	10	13	14
Accidental Death or Missing	0	1	0
Scheduled or Terminal Sacrifice	40	36	36
Survival P Values *(b)*	0.394	0.534	0.442

(a) Terminal kill period weeks 104-106.

(b) The vehicle control column contains the result of the life table trend test; the columns for dosed groups contain the life table pairwise comparisons with the vehicle controls.

TABLE 6. ANALYSIS OF ACINAR-CELL ADENOMA OF THE PANCREAS IN MALE RATS

	Vehicle Control	250 mg/kg	500 mg/kg
Hyperplasia	37/50	34/50	36/49
Hyperplasia, Multifocal	15/50	18/50	25/49
Adenoma, Single *(a)*	12/50 (24%)	15/50 (30%)	15/49 (31%)
Adenoma, Multiple *(a)*	10/50 (20%)	12/50 (24%)	22/49 (45%)
Overall	22/50 (44%)	27/50 (54%)	37/49 (76%)
Adjusted	53.6%	58.7%	82.2%
Terminal	19/38 (50%)	27/46 (59%)	32/40 (80%)
Life Table Test	P=0.003	P=0.548	P=0.007
Incidental Tumor Test	P=0.001	P=0.353	P=0.001

(a) Historical incidence of acinar-cell adenomas or carcinomas (combined) at study laboratory (mean ± SD): 14/298, (5%±9%); historical incidence in NTP studies: 47/1,086 (4%±7%).

III. RESULTS: RATS—TWO-YEAR STUDIES

Preputial Gland: Tumors observed with statistically significant ($P<0.05$) positive trends in male rats include cystadenocarcinoma, all adenocarcinoma, and adenocarcinoma or carcinoma combined (Table 7). Results of the pairwise comparisons with the controls were not statistically significant, and the combined incidence of adenomas, adenocarcinomas, or carcinomas was not statistically significant.

In female rats, clitoral tumors did not occur in statistically significant proportions: control, 2/50, 4%; low-dose, 0/50; high-dose, 5/50, 10%.

Eye: Increased incidences of retinopathy and cataracts were observed in high-dose male rats (retinopathy: control, 1/50, 2%, low-dose, 0/50; high-dose, 20/50, 40%; cataracts: control, 0/50; low-dose, 0/50; high-dose, 13/50, 26%). In female rats, retinopathy was found in 0/50 control, 18/50 (36%) of the low-dose, and 1/50 (2%) of the high-dose groups. Cataracts were seen in 0/50 controls, 3/50 (6%) low-dose, and 0/50 high-dose female rats.

Testis: Interstitial-cell tumors occurred with a statistically significant ($P\leq0.002$) negative trend (control, 48/50, 96%; low-dose, 48/50, 96%; high-dose, 37/50, 74%). The incidence in the high-dose group was statistically significant ($P\leq0.009$) in pairwise comparisons with the controls. There was a significant ($P=0.001$) increase in the incidence of high-dose male rats with interstitial-cell hyperplasia (control, 4/50, 8%; low-dose, 2/50, 4%; high-dose, 17/50, 34%).

TABLE 7. ANALYSIS OF PREPUTIAL GLAND TUMORS IN MALE RATS

	Vehicle Control	250 mg/kg	500 mg/kg
Adenoma	1/50	0/50	0/50
Cystadenocarcinoma			
Overall	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted	0.0%	0.0%	7.5%
Terminal	0/38 (0%)	0/46 (0%)	3/40 (8%)
Life Table Test	P=0.036	*(a)*	P=0.130
Incidental Tumor Test	P=0.036	*(a)*	P=0.130
Adenocarcinoma			
Overall	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted	0.0%	2.2%	10.0%
Terminal	0/38 (0%)	1/46 (2%)	4/40 (10%)
Life Table Test	P=0.025	P=0.538	P=0.070
Incidental Tumor Test	P=0.025	P=0.538	P=0.070
Carcinoma	1/50	0/50	2/50
Adenocarinoma or Carcinoma			
Overall	1/50 (2%)	1/50 (2%)	6/50 (12%)
Adjusted	2.6%	2.2%	14.3%
Terminal	1/38 (3%)	1/46 (2%)	5/40 (13%)
Life Table Test	P=0.023	P=0.719N	P=0.067
Incidental Tumor Test	P=0.040	P=0.719N	P=0.092
Adenoma, Adenocarinoma, or Carcinoma *(b)*			
Overall	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted	5.3%	2.2%	14.3%
Terminal	2/38 (5%)	1/46 (2%)	5/40 (13%)
Life Table Test	P=0.073	P=0.433N	P=0.150
Incidental Tumor Test	P=0.110	P=0.433N	P=0.194

(a) No values are given because there was no tumor incidence in the dosed group or in the vehicle control group.

(b) Historical incidence at study laboratory (mean ± SD): 11/300 (4%±3%); historical incidence in NTP studies: 42/1,100 (4%±4%).

RESULTS: MICE

SINGLE-DOSE STUDY

All mice that received 4,000 mg/kg and females that received 2,000 mg/kg benzyl acetate were inactive immediately after dosing. All mice that received 4,000 mg/kg and 1/5 males and 2/5 females that received 2,000 mg/kg died; deaths occurred on day 2.

Dose levels of 125, 250, 500, 1,000, and 2,000 mg/kg were selected for mice of both sexes in the 14-day study. The highest dose was selected to insure an adequate dose range for evaluation.

FOURTEEN-DAY STUDY

All male mice that received 2,000 mg/kg were dead by the afternoon of day 3. No other compound-related deaths occurred. Weight changes were not dose related (Table 8). Compound-related clinical signs were observed in high-dose males (ruffled fur, ataxia) and in high-dose females (labored breathing, hyperactivity). Mucosa in the cardiac region of the stomach was roughened in 2/5 males and 5/5 females that received 2,000 mg/kg and in 1/5 females that received 1,000 mg/kg. Based on the mortality data, doses of 62.5, 125, 250, 500, and 1,000 mg/kg for males and 125, 250, 500, 1,000, and 2,000 mg/kg for females were selected for use in the 13-week study.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED BENZYL ACETATE BY GAVAGE FOR 14 DAYS

Dose (mg/kg)	Survival *(a)*	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)
		Initial	Final	Change *(b)*	
Male					
0	4/5 *(c)*	24.0 ± 1.3	25.5 ± 1.2	+ 1.5 ± 0.3	
125	5/5	25.4 ± 1.2	26.4 ± 1.2	+ 1.0 ± 0.0	103.5
250	4/5 *(c)*	24.8 ± 1.0	25.8 ± 1.2	+ 1.0 ± 0.4	101.2
500	5/5	24.0 ± 0.3	25.2 ± 0.6	+ 1.2 ± 0.4	98.8
1,000	4/5 *(c)*	28.5 ± 0.5	30.8 ± 1.1	+ 2.3 ± 0.6	120.8
2,000	0/5 *(d)*	*(e)*	*(e)*	*(e)*	
Female					
0	5/5	20.4 ± 0.5	22.0 ± 0.8	+ 1.6 ± 0.5	
125	5/5	19.6 ± 0.9	19.8 ± 0.7	+ 0.2 ± 0.6	90.0
250	5/5	20.0 ± 0.8	21.2 ± 1.1	+ 1.2 ± 0.4	96.4
500	5/5	19.2 ± 0.6	20.2 ± 0.5	+ 1.0 ± 0.4	91.8
1,000	5/5	19.4 ± 0.6	20.0 ± 0.9	+ 0.6 ± 0.5	90.9
2,000	3/5 *(c)*	20.0 ± 0.6	21.7 ± 0.7	+ 1.7 ± 0.3	98.6

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change to the group ± standard error of the mean.
(c) Deaths due to gavage error.
(d) Deaths occurred by day 3.
(e) No data are presented due to the 100% mortality in this group.

THIRTEEN-WEEK STUDY

Eight of the ten female mice that received 2,000 mg/kg died (Table 9); one of these deaths was caused by gavage error. Deaths in all other male and female dosed and control groups were also considered to be the result of gavage error. Compound-related clinical signs observed in high-dose mice included trembling, inactivity, labored breathing, and depressed body temperature. No compound-related gross or microscopic pathologic effects were observed.

Doses of benzyl acetate selected for mice on the chronic study were 500 and 1,000 mg/kg body weight in corn oil by gavage.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED BENZYL ACETATE BY GAVAGE FOR 13 WEEKS

Dose (mg/kg)	Survival *(a)*	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)
		Initial	Final	Change *(b)*	
Male					
0	9/10 *(c)*	24.2 ± 0.5	32.7 ± 1.0	+ 8.5 ± 0.7	
62.5	9/10 *(c)*	23.1 ± 0.5	32.6 ± 1.2	+ 9.5 ± 0.9	99.7
125	9/10 *(c)*	23.2 ± 0.7	32.7 ± 1.3	+ 9.5 ± 0.9	100.0
250	10/10	23.6 ± 0.5	33.5 ± 0.9	+ 9.9 ± 0.7	102.4
500	9/10 *(c)*	22.7 ± 0.8	33.6 ± 1.6	+ 10.9 ± 1.2	102.8
1,000	8/10 *(c)*	23.5 ± 0.3	34.8 ± 1.5	+ 11.3 ± 1.3	106.4
Female					
0	6/10 *(c)*	18.8 ± 0.5	25.8 ± 1.3	+ 7.0 ± 0.9	
125	9/10 *(c)*	17.0 ± 0.2	24.3 ± 0.5	+ 7.3 ± 0.4	94.2
250	9/10 *(c)*	17.8 ± 0.4	24.8 ± 0.7	+ 7.0 ± 0.5	96.1
500	6/10 *(c)*	17.8 ± 0.5	24.3 ± 0.8	+ 6.5 ± 0.7	94.2
1,000	7/10 *(c)*	19.3 ± 0.6	27.4 ± 0.9	+ 8.1 ± 0.6	106.2
2,000	2/10 *(d)*	18.0 ± 1.0	25.5 ± 0.5	+ 7.5 ± 0.5	98.8

(a) Number surviving/number initially in the group. All calculations are based on those animals surviving to the end of the study.
(b) Mean weight change of the group ± standard error of the mean.
(c) Deaths due to gavage error.
(d) One of eight deaths was due to gavage error.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout the study, mean body weights of dosed and control male mice were comparable (Table 10 and Figure 3). After week 20, mean body weights of low- and high-dose female mice were slightly higher than those of the controls.

Survival

Estimates of the probabilities of survival of male and female mice administered benzyl acetate by gavage at the doses of these studies, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. The survival of the high-dose group of female mice was significantly increased when compared with that of the controls group (P=0.005; Table 11). No other significant differences in survival were observed between any groups of either sex. Two low-dose males, one high-dose male, four low-dose females, and one high-dose female were accidently killed. The animals were censored from the statistical analysis of survival at the date of death.

In male mice, 38/50 (76%) of the controls, 33/50 (66%) of the low-dose, and 39/50 (78%) of the high-dose group lived to the termination period of the study at 104-106 weeks. In female mice, 15/50 (30%) of the controls, 18/50 (36%) of the low-dose, and 30/50 (60%) of the high-dose group lived to the termination period of the study at 104-106 weeks. The survival data include one low-dose male that died during the termination period. For statistical purposes, this animal was considered to have been killed at the end of the study.

Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2. Appendix E, Tables E3 and E4 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

Liver: In male mice, hepatocellular adenomas occurred with a statistically significant positive trend (Table 12). Results of pairwise comparisons with the controls were significant for both the low-dose and high-dose groups. Adenomas or carcinomas (combined) in male mice also occurred with a significant positive trend, and the results of pairwise comparisons were significant for the high-dose group. In female mice, adenomas were observed in a statistically significant positive trend. The results of pairwise comparisons with the controls were significant for the high-dose group (P=0.013, incidental tumor test). Adenomas or carcinomas (combined) occurred with a significant positive trend, and the results of pairwise comparisons with the controls were significant for the high-dose group (Table 12).

One additional neoplasm was observed in the liver of a high-dose male mouse. However, because this neoplasm was necrotic as a result of obstructed blood vessels, it was not possible to determine whether this neoplasm was an adenoma or carcinoma.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ACETATE

Weeks on Study	Control		500 mg/kg			1,000 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	24.1	50	24.2	100	50	24.2	100	50
1	25.1	50	25.8	103	50	26.3	105	50
2	27.2	50	27.6	101	50	27.7	102	50
3	27.9	50	28.6	103	50	28.3	101	50
4	28.4	50	29.3	103	50	28.9	102	50
5	29.8	50	30.1	101	50	29.7	100	50
6	30.5	49	30.7	101	50	30.7	101	50
7	31.4	49	31.7	101	50	31.7	101	50
8	31.5	49	31.7	101	50	32.1	102	50
9	31.5	49	32.2	102	50	32.4	103	50
10	32.9	49	32.2	98	49	32.6	99	50
11	33.8	49	33.4	99	49	33.6	99	50
13	33.5	49	33.7	101	49	33.4	100	50
14	34.4	49	34.1	99	49	33.6	98	50
19	34.3	49	36.3	106	48	36.2	106	50
22	36.5	49	37.3	102	48	36.9	101	50
26	38.6	49	39.4	102	48	39.5	102	48
31	41.2	46	41.3	100	48	41.8	101	48
35	42.5	45	43.8	103	48	42.9	101	48
40	43.8	44	44.6	102	47	44.1	101	48
44	44.0	44	44.7	102	47	44.3	101	48
49	43.8	44	44.3	101	46	43.8	100	48
53	46.2	44	47.1	102	45	46.0	100	48
57	46.1	44	46.5	101	45	46.7	101	48
61	45.3	44	45.7	101	45	45.7	101	48
66	45.1	44	46.3	103	45	45.4	101	47
71	45.1	43	45.0	100	44	46.4	103	47
75	45.7	42	45.6	100	43	46.3	101	46
79	44.5	42	45.2	102	43	46.4	104	46
83	45.4	42	45.3	100	43	46.6	103	46
87	45.3	41	45.1	100	43	45.9	101	46
93	44.7	39	43.5	97	37	45.4	102	42
97	46.3	38	45.0	97	35	46.2	100	41
102	44.8	38	41.7	93	33	44.1	98	40
104	44.5	38	42.0	94	33	43.3	97	39
FEMALE								
0	19.6	50	19.7	101	50	19.4	99	50
1	18.7	50	19.9	106	50	20.8	111	50
2	21.7	50	21.4	99	50	21.4	99	50
3	22.2	50	22.2	100	50	22.1	100	50
4	22.4	50	22.1	99	50	22.7	101	50
5	22.7	50	22.8	100	48	23.2	102	50
6	24.1	50	23.4	97	48	23.8	99	50
7	24.0	50	23.9	100	48	24.3	101	50
8	23.7	50	24.2	102	48	24.4	103	50
9	24.3	50	24.0	99	47	24.7	102	50
10	24.6	50	24.7	100	47	25.1	102	50
11	25.0	50	25.3	101	47	25.5	102	50
13	25.3	50	25.1	99	47	25.4	100	50
14	25.5	50	25.2	99	47	25.5	100	50
19	25.2	49	26.0	103	47	27.6	110	50
22	26.7	48	27.6	103	47	28.1	105	48
26	28.8	48	29.1	101	47	30.1	105	48
31	30.1	48	30.9	103	47	31.4	104	48
35	32.3	48	32.2	100	47	33.3	103	48
40	32.2	47	33.9	105	46	34.1	106	48
44	33.6	47	34.9	104	45	34.9	104	48
49	33.8	47	34.8	103	45	35.5	105	48
53	35.1	47	37.7	107	44	37.8	108	48
57	35.6	46	38.0	107	42	38.0	107	47
61	35.5	46	37.6	106	42	38.0	107	47
66	34.3	44	36.9	108	42	38.3	112	46
71	34.7	40	38.6	111	40	38.5	111	44
75	34.6	38	40.1	116	35	39.9	115	42
79	33.8	34	40.2	119	33	40.1	119	40
83	35.7	31	40.2	113	30	41.1	115	38
87	34.4	28	39.8	116	29	40.9	119	36
93	34.9	20	36.7	105	27	40.8	117	33
97	35.1	17	37.4	107	25	42.3	121	30
102	34.6	15	36.5	105	20	39.9	115	30
104	34.8	15	36.9	106	18	38.8	111	30

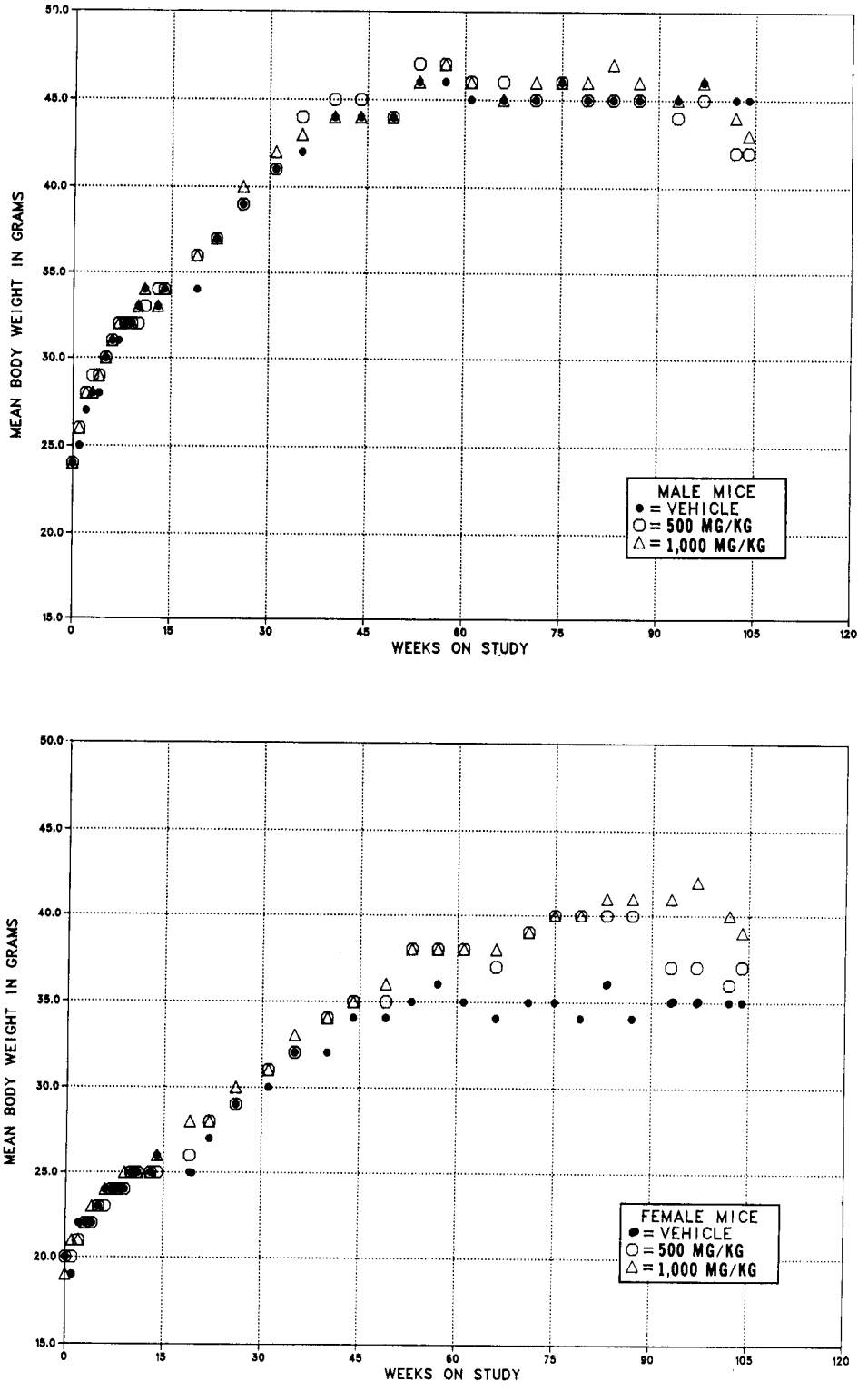
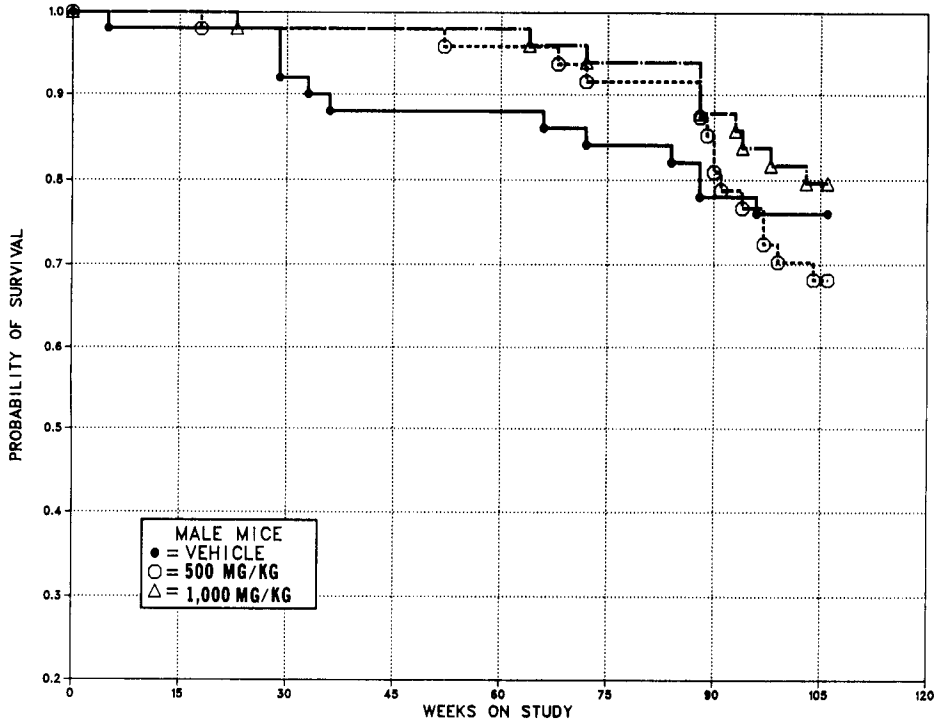


Figure 3. Growth Curves for Mice Administered Benzyl Acetate in Corn Oil by Gavage



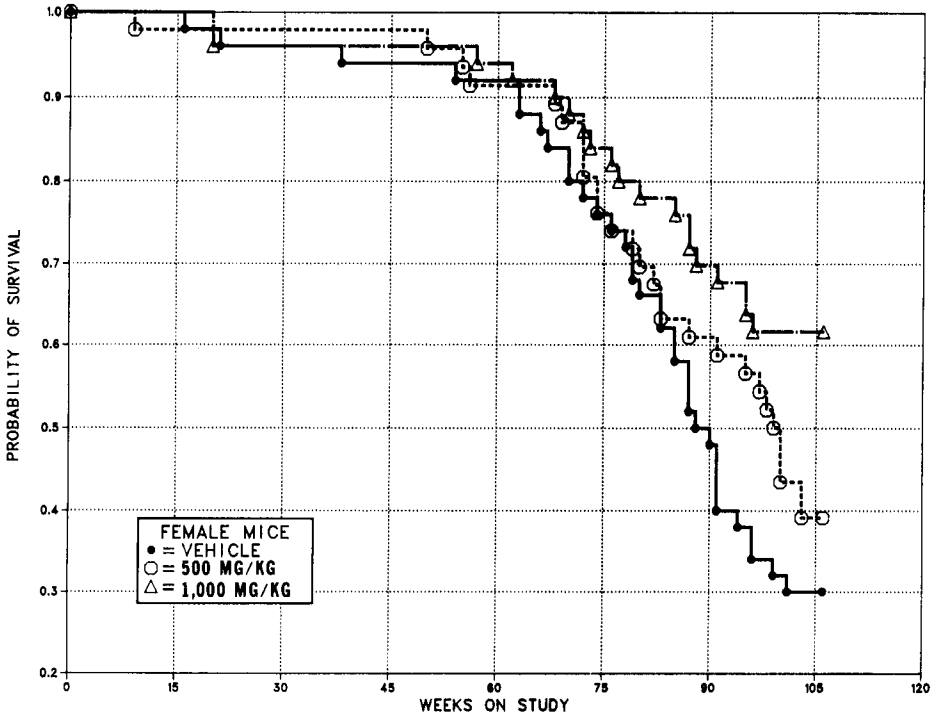


Figure 4. Kaplan-Meier Survival Curves for Mice Administered Benzyl Acetate in Corn Oil by Gavage

TABLE 11. SURVIVAL OF B6C3F$_1$ MICE IN THE TWO-YEAR GAVAGE STUDIES OF BENZYL ACETATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Male *(a)*			
Animals Initially in Study	50	50	50
Natural Death or Moribund Sacrifice	12	14	10
Accidental Death or Missing	0	3	1
Scheduled or Terminal Sacrifice	38	33	39
Survival P Values *(b)*	0.628	0.855	0.714
Female *(a)*			
Animals Initially in Study	50	50	50
Natural Death or Moribund Sacrifice	35	28	19
Accidental Death or Missing	0	4	1
Scheduled or Terminal Sacrifice	15	18	30
Survival P Values *(b)*	0.033	0.313	0.005

(a) Terminal kill period weeks 104-106.

(b) The vehicle control column contains the result of the life table trend test; the columns for dosed groups contain the life table pairwise comparisons with the vehicle controls.

TABLE 12. ANALYSIS OF LIVER TUMORS IN MICE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Males			
Adenoma			
Overall	0/50 (0%)	5/49 (10%)	13/50 (26%)
Adjusted	0.0%	13.0%	33.3%
Terminal	0/38 (0%)	3/33 (9%)	13/39 (33%)
Life Table Test	P<0.001	P=0.030	P<0.001
Incidental Tumor Test	P<0.001	P=0.023	P<0.001
Carcinoma			
Overall	10/50 (20%)	14/49 (29%)	12/50 (24%)
Adjusted	24.3%	35.9%	25.8%
Terminal	7/38 (18%)	9/33 (27%)	5/39 (13%)
Life Table Test	P=0.427	P=0.183	P=0.463
Incidental Tumor Test	P=0.536	P=0.379	P=0.548N
Adenoma or Carcinoma *(b)*			
Overall	10/50 (20%)	18/49 (37%)	23/50 (46%)
Adjusted	24.3%	45.1%	49.8%
Terminal	7/38 (18%)	12/33 (36%)	16/39 (41%)
Life Table Test	P=0.013	P=0.042	P=0.014
Incidental Tumor Test	P=0.009	P=0.098	P=0.019
Females			
Adenoma			
Overall	0/50 (0%)	0/50 (0%)	6/50 (12%)
Adjusted	0.0%	0.0%	17.4%
Terminal	0/15 (0%)	0/18 (0%)	3/30 (10%)
Life Table Test	P=0.012	*(a)*	P=0.067
Incidental Tumor Test	P=0.002	*(a)*	P=0.013
Carcinoma			
Overall	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted	6.7%	0.0%	12.6%
Terminal	1/15 (7%)	0/18 (0%)	3/30 (10%)
Life Table Test	P=0.209	P=0.464N	0.401
Incidental Tumor Test	P=0.150	P=0.464N	0.302
Adenoma or Carcinoma *(c)*			
Overall	1/50 (2%)	0/50 (0%)	10/50 (20%)
Adjusted	6.7%	0.0%	28.7%
Terminal	1/15 (7%)	0/18 (0%)	6/30 (20%)
Life Table Test	P=0.007	P=0.464N	P=0.050
Incidental Tumor Test	P=0.001	P=0.464N	P=0.008

(a) No values are given because there was no tumor incidence in the dosed group or in the vehicle control group.

(b) Historical incidence at study laboratory (mean ± SD): 109/208 (37%±12%); historical incidence in NTP studies: 357/1,091 (33%±10%).

(c) Historical incidence at study laboratory (mean ± SD): 18/300 (6%±3%); historical incidence in NTP studies: 74/1,092 (7%±4%).

III. RESULTS: MICE—TWO-YEAR STUDIES

Forestomach: Hyperplasia of the forestomach occurred at increased incidence in dosed mice of either sex (Table 13). The incidences in dosed male mice and high-dose female mice were significantly ($P<0.005$) higher than those of the controls.

Squamous cell papillomas or carcinomas of the forestomach were increased in male mice. Squamous cell papillomas were also found in four high-dose female mice.

Multiple organs: Suppurative inflammation or abscesses of the ovaries, uterus, mesentery, peritoneum, or multiple organs were found in 26/35 control, 14/32 low-dose, and 8/20 high-dose female mice that died before the terminal kill.

Uterus/Endometrium: Cystic hyperplasia was found in 26/50 (52%) control, 28/50 (56%) low-dose, and 37/50 (74%) high-dose female mice.

TABLE 13. ANALYSIS OF FORESTOMACH LESIONS IN MICE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Males			
Epithelial Hyperplasia	1/49 (2%)	7/48 (15%) (b)	22/49 (45%) (b)
Squamous Cell Papilloma			
Overall	3/49 (6%)	3/48 (6%)	9/49 (18%)
Adjusted	7.9%	9.1%	23.1%
Terminal	3/38 (8%)	3/33 (9%)	9/39 (23%)
Life Table Test	P=0.038	P=0.597	P=0.065
Incidental Tumor Test	P=0.038	P=0.597	P=0.065
Squamous Cell Carcinoma	1/49 (2%)	1/48 (2%)	2/49 (4%)
Squamous Cell Papilloma or Carcinoma *(c)*			
Overall	4/49 (8%)	4/48 (8%)	11/49 (22%)
Adjusted	10.0%	11.3%	28.2%
Terminal	3/38 (8%)	3/33 (9%)	11/39 (28%)
Life Table Test	P=0.032	P=0.588	P=0.052
Incidental Tumor Test	P=0.028	P=0.619	P=0.051
Females			
Epithelial Hyperplasia	1/49 (2%)	7/48 (15%) (b)	22/49 (45%) (b)
Squamous Cell Papilloma *(d)*			
Overall	0/50 (0%)	0/50 (0%)	4/48 (8%)
Adjusted	0.0%	0.0%	13.3%
Terminal	0/15 (0%)	0/18 (0%)	4/30 (13%)
Life Table Test	P=0.054	*(a)*	P=0.180
Incidental Tumor Test	P=0.054	*(a)*	P=0.180

(a) No values are given because there was no tumor incidence in the dosed group or in the vehicle control group.

(b) Significantly ($P<0.05$) higher than controls.

(c) Historical incidence at study laboratory (mean ± SD): 2/296 (0.7±2%); historical incidence in NTP studies: 14/1,070 (1%±2%).

(d) Historical incidence at study laboratory (mean ± SD): 2/297 (0.7±1%); historical incidence in NTP studies: 3/1,073 (0.3%±0.7%).

IV. DISCUSSION AND CONCLUSIONS

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Administration of benzyl acetate to rats for two years at doses of 250 or 500 mg/kg and to mice at doses of 500 or 1,000 mg/kg did not adversely affect survival or mean body weight gain. However, in both the 14-day and the 13-week studies deaths and/or mean body weight gain depressions occurred among rats that received 1,000 mg/kg and among mice that received 2,000 mg/kg indicating that the doses selected in the 2-year studies were sufficiently challenging for carcinogenicity. Furthermore, it was shown that the doses used for rats and mice in the 2-year studies did not saturate their capacity to absorb, metabolize, and excrete benzyl acetate (Appendix H).

Survivals were generally comparable among groups; however, only 15/50 (30%) of the control female mice and 18/50 (36%) of the low-dose female mice lived to the end of the study. An infection, resulting in suppurative inflammation or abscesses of the ovaries, uterus, mesentery, peritoneum, or multiple organs, was the probable cause of death in 26/35 control, 14/32 low-dose, and 8/20 high-dose females that died before the terminal kill. The incidence of ovarian abscesses and suppurative inflammation in the genital tract of the female mice was inversely related to dose. Although the contribution of benzyl acetate to the decreased incidence of female mice with ovarian abscesses is not clear, this effect may be related to the bacteriostatic properties of its metabolites (benzyl alcohol and benzoic acid).

The increased incidence of high-dose male rats with retinopathy and cataracts or of low-dose female rats with retinopathy was not considered to be related to administration of benzyl acetate. These effects have been correlated at this laboratory with the proximity of the rats to fluorescent light. (See Chignell et al., 1981; Greenman et al., 1982.) Cage positions and incidences of eye lesions are shown in Appendix M, Table M1. High-dose male and low-dose female rats were housed closest to the light source in this study.

Acinar-cell adenomas in the pancreas of male rats were considered to be related to the gavage administration of benzyl acetate. A statistically significant ($P \leq 0.003$) positive trend was observed in the incidences of male rats with acinar-cell adenomas of the pancreas, and the incidence in the high-dose group (37/49, 76%) was significantly ($P \leq 0.007$) higher than the incidence in the vehicle controls (22/50, 44%). The incidence of acinar-cell tumors in the low-dose group (27/50, 54%) was not significantly ($P > 0.10$) greater than that in the vehicle controls. The acinar-cell adenomas were more often multiple in the treated animals. Acinar-cell hyperplasia of the pancreas was observed in 37/50 control, 34/50 low-dose, and 36/49 high-dose male rats. The incidences of acinar-cell adenomas of the pancreas reported here (22/50; 27/50; 37/49) are considerably higher than those reported at the June 16, 1982 peer review meeting (3/50; 8/50; 8/49). This difference was due to the effect of subsequent sampling and diagnoses of the proliferative lesions of the pancreas. In a study conducted for NTP on pancreatic tissue from several groups of corn oil vehicle control animals, including those for the benzyl acetate study, it was found that the incidence of the proliferative lesions observed were positively related to the quantity of tissue examined. For this reason, all pancreata remaining in the wet tissues of all groups of male rats in the benzyl acetate study were embedded flat and sectioned. This effectively increased the quantity of tissue examined, resulting in the higher incidence of acinar-cell adenomas observed and reported here. However, this increase in the incidence of adenoma of the pancreatic acini of male rats did not alter the conclusion that benzyl acetate given in corn oil by gavage was associated with the increased incidence of this neoplasm in male F344/N rats. The historical rate of acinar-cell adenomas in 1,086 vehicle controls (4.3%; Appendix F, Table F3) is on average higher than that diagnosed in 1,667 untreated male F344/N rats (0.2%). The rate of proliferative acinar-cell lesions has been found in other NTP studies to be higher in male rats receiving corn oil vehicle than in the untreated controls (Boorman and Eustis, 1984). In this study an effort was made to include all pancreatic tissue for examination to eliminate any possibility of a sampling bias. Additional lesions were found in all dose groups upon examination of the wet tissues. This explains why the overall rates are higher than the historical rates. The examination of the entire pancreas confirmed the trend found in the original examination. The exact biological potential of the hyperplasias versus the acinar-cell adenomas has not been established, and this subject is currently under study by the NTP. Many pathologists currently agree that hyperplasias and adenomas are identifiable stages in the pathogenesis of lesions in the exocrine pancreas. Whether the increased incidence and multiplicity of these

lesions in the treated animals is due to benzyl acetate, the vehicle, or a combination of the two, is not known; yet the major variable in this study is benzyl acetate, and until more experimental information is gathered, these lesions are considered to be related to exposure to benzyl acetate.

Hepatocellular adenomas occurred with a statistically significant positive trend ($P<0.05$) in mice of either sex (Table 12). Results of pairwise comparisons of the incidences for high-dose males and for high-dose females were significant (males, $P<0.001$; females, $P<0.05$). The absence of hepatocellular adenomas in the concurrent female control groups may be due in part to early mortality; however, all adenomas in the high-dose group were observed between week 87 and the end of the study and 58% of the control females survived to at least this age. Since the incidences of high-dose males and females with adenomas are significantly greater ($P<0.05$) than those observed in concurrent controls, and are also elevated relative to historical gavage controls for this laboratory (males: 36/298, 12.1%; range 0-22%; females: 11/300, 3.7%; range 0-8%; Appendix F, Tables F5 and F6), these increases are considered to be associated with administration of benzyl acetate. The incidences of dosed male mice and high-dose female mice with hepatocellular carcinomas were elevated slightly, but not significantly (males: control, 10/50, 20%; low-dose, 14/49, 29%; and high-dose, 12/50, 24%; females: control, 1/50, 2%; low-dose, 0/50; and high-dose, 4/50, 8%).

Squamous cell papillomas and squamous cell papillomas or carcinomas (combined) of the forestomach occurred with a positive trend ($P<0.05$) in male mice; the incidence of squamous cell papillomas was also elevated in the high-dose female mice (Table 13). The increased incidence of forestomach tumors in both the high-dose male and high-dose female mice was considerably higher than the historical corn oil gavage control rate at this laboratory (males: 2/296, 0.7%; females: 2/297, 0.7%) and throughout the Carcinogenesis Program (males: 14/1,070, 1.3%; females: 3/1,073, 0.3%; Appendix F, Tables F3 and F4). Forestomach hyperplasia also occurred at increased incidences in dosed mice of either sex (Table 13). Both squamous cell papillomas or carcinomas and hyperplasia of the forestomach were probably associated with the administration of benzyl acetate. Since benzyl acetate was given by gavage and is a biologically reactive chemical, the increased incidence of hyperplasia in dosed mice may have been the result of direct action of the chemical at the site of deposition in the forestomach.

Malignant preputial gland tumors occurred with a statistically significant ($P<0.05$) positive trend in male rats. However, since the combined incidence of adenomas, adenocarcinomas, or carcinomas was not statistically significant, these tumors are not considered to be associated with benzyl acetate administration. The combined incidence of clitoral gland adenomas or carcinomas in female rats was not statistically increased. The incidences in the high dose rats of either sex (males: 6/50, 12%; females: 5/50, 10%) were higher than the corresponding historical corn oil gavage control rates at this laboratory (males: 11/300, 3.7%; females: 6/300, 2.0%) and throughout the Carcinogenesis Program (males: 42/1,100, 3.8%; females: 27/1,100, 2.5%; Appendix F, Tables F1 and F2).

Testicular (interstitial-cell) tumors in male rats were observed with a negative trend and the incidence in the high-dose group was lower than that in the controls. Conversely, there was an increase in the incidence of high-dose male rats with interstitial-cell hyperplasia. These two lesions are essentially similar, differing mainly in size. Interstitial-cell tumors are generally larger with widespread necrosis. The diagnosis of a lesion as interstitial-cell hyperplasia or interstitial-cell tumor may vary among pathologists. To better assess the potential relationship between benzyl acetate administration and the incidence of male rats with these lesions, the combined incidence was considered more appropriate, and was not statistically different from that of the controls. Neither the decrease in testicular tumors nor the increase in interstitial-cell hyperplasia was considered to be related to the administration of this chemical. Rather, the tumors appear to be associated with the aging process in these animals.

Cystic hyperplasia of the uterus/endometrium was observed in 26/50 (52%) control, 28/50 (56%) low-dose, and 37/50 (74%) high-dose female mice. Because of the infection at this site, this increased incidence could not be clearly related to the administration of benzyl acetate.

IV. DISCUSSION AND CONCLUSIONS

Benzyl acetate was not mutagenic in several microbial assays and did not induce sister chromatid exchanges or a clear increase in chromosomal aberrations in CHO cells (see Introduction), but it was mutagenic in cultured mammalian cells (the L5178Y/$TK^{+/-}$ mouse lymphoma assay) in the presence, but not in the absence, of Aroclor 1254-induced rat liver S9 (Appendix G). Although the spontaneous mutation frequency for the mouse lymphoma test in the presence of S9 was slightly high, benzyl acetate produced a dose-related, fourfold increase in the mutation frequency compared to that of the control, and the results were reproducible. The reason for the positive response in the mouse lymphoma assay and the lack of response in the other assays is not known. However, because S9 was required suggests that a metabolite of benzyl acetate was likely responsible for the observed mutagenicity.

Under the conditions of these studies, benzyl acetate increased the incidence of acinar-cell adenomas of the exocrine pancreas in male F344/N rats; the gavage vehicle may have been a contributing factor. No evidence of carcinogenicity* was found for female F344/N rats. For male and female $B6C3F_1$ mice there was some evidence of carcinogenicity in that benzyl acetate caused increased incidences of hepatocellular adenomas and squamous cell neoplasms of the forestomach.

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

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APPENDIX A
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	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%)	1 (2%)
KERATOACANTHOMA	2 (4%)	4 (8%)	2 (4%)
*SUBCUT TISSUE	(50)	(50)	(50)
TRICHOEPITHELIOMA		1 (2%)	
SARCOMA, NOS	3 (6%)	1 (2%)	
FIBROMA	3 (6%)	11 (22%)	5 (10%)
LIPOMA			1 (2%)
NEURILEMOMA, MALIGNANT	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(48)
ALVEOLAR/BRONCHIOLAR ADENOMA		2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA, METAS	1 (2%)		
SARCOMA, NOS, METASTATIC	1 (2%)		1 (2%)
LIPOSARCOMA, METASTATIC			1 (2%)
NEURILEMOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MONOCYTIC LEUKEMIA	5 (10%)	5 (10%)	6 (12%)
CIRCULATORY SYSTEM			
*MESENTERY	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(50)	(50)
SARCOMA, NOS			1 (2%)
#LIVER	(49)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	1 (2%)	2 (4%)
HEPATOCELLULAR CARCINOMA		1 (2%)	
#PANCREAS	(50)	(50)	(49)
ACINAR-CELL ADENOMA	22 (44%)	27 (54%)	37 (76%)
#STOMACH	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
#SMALL INTESTINE	(49)	(49)	(49)
MUCINOUS ADENOCARCINOMA			1 (2%)
#JEJUNUM	(49)	(49)	(49)
MUCINOUS ADENOCARCINOMA			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
CARCINOMA, NOS	1 (2%)	2 (4%)	
ADENOMA, NOS	7 (14%)	10 (20%)	7 (14%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	1 (2%)	
CORTICAL CARCINOMA			1 (2%)
PHEOCHROMOCYTOMA	8 (16%)	5 (10%)	8 (16%)
#THYROID	(50)	(50)	(49)
FOLLICULAR-CELL ADENOMA	1 (2%)	2 (4%)	
FOLLICULAR-CELL CARCINOMA	4 (8%)	2 (4%)	2 (4%)
C-CELL ADENOMA	3 (6%)		2 (4%)
C-CELL CARCINOMA	3 (6%)	2 (4%)	3 (6%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#PARATHYROID	(48)	(47)	(41)
ADENOMA, NOS	1 (2%)		
#PANCREATIC ISLETS	(50)	(50)	(49)
ISLET-CELL ADENOMA	6 (12%)	5 (10%)	5 (10%)
ISLET-CELL CARCINOMA	3 (6%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS			2 (4%)
FIBROADENOMA	4 (8%)	1 (2%)	2 (4%)
*BULBOURETHRAL GLAND	(50)	(50)	(50)
CYSTADENOMA, NOS			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		2 (4%)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
CYSTADENOCARCINOMA, NOS			3 (6%)
SARCOMA, NOS			1 (2%)
#PROSTATE	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	48 (96%)	48 (96%)	37 (74%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MUSCLE OF BACK	(50)	(50)	(50)
LIPOSARCOMA	1 (2%)		

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
LIPOSARCOMA			1 (2%)
*PELVIS	(50)	(50)	(50)
LIPOSARCOMA	1 (2%)		
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	2 (4%)		1 (2%)
ALL OTHER SYSTEMS			
SITE UNKNOWN			
NEURILEMOMA		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	6	3	4
MORIBUND SACRIFICE	7	2	5
SCHEDULED SACRIFICE	5		
TERMINAL SACRIFICE	32	45	40
ACCIDENTALLY KILLED, NOS			1

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	50	48
TOTAL PRIMARY TUMORS	136	137	138
TOTAL ANIMALS WITH BENIGN TUMORS	48	50	47
TOTAL BENIGN TUMORS	108	120	108
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	14	24
TOTAL MALIGNANT TUMORS	25	16	27
TOTAL ANIMALS WITH SECONDARY TUMORS#	3		2
TOTAL SECONDARY TUMORS	3		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	1	3
TOTAL UNCERTAIN TUMORS	3	1	3

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	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%)	1 (2%)	
SEBACEOUS ADENOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA		1 (2%)	
RHABDOMYOSARCOMA	1 (2%)		
NEURILEMOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)
C-CELL CARCINOMA, METASTATIC	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LYMPHOCYTIC LEUKEMIA		1 (2%)	
MONOCYTIC LEUKEMIA	2 (4%)	2 (4%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	2 (4%)	1 (2%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(48)
CARCINOMA, NOS	1 (2%)	3 (6%)	1 (2%)
ADENOMA, NOS	18 (36%)	10 (20%)	14 (29%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA		2 (4%)	1 (2%)
PHEOCHROMOCYTOMA	1 (2%)	4 (8%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
GANGLIONEUROMA			1 (2%)
#THYROID	(50)	(50)	(49)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA		2 (4%)	1 (2%)
C-CELL ADENOMA	6 (12%)	4 (8%)	4 (8%)
C-CELL CARCINOMA	4 (8%)	5 (10%)	4 (8%)
CYSTADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(49)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)
PAPILLARY ADENOCARCINOMA			1 (2%)
CYSTADENOMA, NOS	1 (2%)		
FIBROADENOMA	16 (32%)	17 (34%)	16 (32%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		2 (4%)
ADENOMA, NOS			3 (6%)
#UTERUS	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ADENOCARCINOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	12 (24%)	9 (18%)	18 (36%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	3 (6%)	3 (6%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
CARCINOMA, NOS			1 (2%)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)	3 (6%)	
#OVARY	(50)	(50)	(50)
GRANULOSA-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
ADENOSQUAMOUS CARCINOMA		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)
DIAPHRAGM			
ADENOCARCINOMA, NOS, METASTATIC		1	

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	3	7	5
MORIBUND SACRIFICE	8	7	9
SCHEDULED SACRIFICE	5		
TERMINAL SACRIFICE	34	35	36
ACCIDENTALLY KILLED, NOS		1	

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	43	44	44
TOTAL PRIMARY TUMORS	75	76	76
TOTAL ANIMALS WITH BENIGN TUMORS	38	34	39
TOTAL BENIGN TUMORS	59	52	57
TOTAL ANIMALS WITH MALIGNANT TUMORS	15	17	16
TOTAL MALIGNANT TUMORS	15	21	18
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	2	
TOTAL SECONDARY TUMORS	2	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	3	1
TOTAL UNCERTAIN TUMORS	1	3	1

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	104	093	101	104	104	104	089	106	096	061	106	106	093	106	078	089	061	106	102	106	106	083	061	061	106
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA																				X					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																X					X				
FIBROMA													X												
NEURILEMOMA, MALIGNANT			X																						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA, META																									
SARCOMA, NOS, METASTATIC																									
NEURILEMOMA, METASTATIC			X																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA	X	X		X	X	X			X	X	X			X			X		X	X	X		X	X	X
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS				X																					
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS																			X						
ADENOMA, NOS																		X						X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA		X																	X						
PHEOCHROMOCYTOMA																							X	X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA																									
C-CELL CARCINOMA								X												X					
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																			X						
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA							X													X					
ISLET-CELL CARCINOMA						X				X													X		
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA					X			X					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	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS					X																				
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA, NOS																								X	
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOSARCOMA		X																							
OSTEOSARCOMA																									
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
LIPOSARCOMA		X																							
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS	X																								
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA													X					X							

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	110	105	106	106	109	116	106	106	106	093	106	106	106	106	106	106	106	106	106	101	106	094	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
KERATOACANTHOMA																						X				2
SUBCUTANEOUS TISSUE	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SARCOMA, NOS					X																					3
FIBROMA	X						X																			3
NEURILEMOMA, MALIGNANT																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL CARCINOMA, META																									X	1
SARCOMA, NOS, METASTATIC					X																					1
NEURILEMOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NEOPLASTIC NODULE															X											1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA		X					X	X	X			X					X									22
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS																										1
ADENOMA, NOS				X			X			X			X												X	7
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																										1
PHEOCHROMOCYTOMA							X			X	X					X						X				6
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA												X														1
FOLLICULAR-CELL CARCINOMA													X			X						X			X	4
C-CELL ADENOMA			X											X									X			5
C-CELL CARCINOMA																							X			3
PARATHYROID	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		48
ADENOMA, NOS																										1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA				X							X				X						X					6
ISLET-CELL CARCINOMA																										3
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA				X																						4
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS																										1
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
ADENOMA, NOS								X																		1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
MUSCLE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
LIPOSARCOMA																										1
OSTEOSARCOMA		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*
LIPOSARCOMA																										1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MESOTHELIOMA, NOS																	X									2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MONOCYTIC LEUKEMIA															X					X			X			5

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: *TUMOR INCIDENCE*
N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
': *NO TISSUE INFORMATION SUBMITTED*
C NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M ANIMAL MISSING
B NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	081	105	103
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA								X																	
KERATOACANTHOMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRICHOEPITHELIOMA									X																
SARCOMA, NOS																									
FIBROMA					X		X					X												X	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA									X																
ALVEOLAR/BRONCHIOLAR CARCINOMA								X																	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	-
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
HEPATOCELLULAR CARCINOMA																						X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA		X	X				X	X			X	X	X	X	X	X	X	X					X	X	X
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA						X																			
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS		X																X							
ADENOMA, NOS				X	X			X								X				X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
PHEOCHROMOCYTOMA																		X				X			X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA											X														
FOLLICULAR-CELL CARCINOMA																			X						
C-CELL CARCINOMA																					X				
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA				X	X		X												X						
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	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
ADENOCARCINOMA, 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
SQUAMOUS CELL CARCINOMA								X																	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA					X																			X	
SITE UNKNOWN																									
NEURILEMMOMA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	103	105	105	105	085	106	106	106	106	106	106	106	106	106	091	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
KERATOACANTHOMA		X																				X		X		4
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
TRICHOEPITHELIOMA																										1
SARCOMA, NOS																										1
FIBROMA	X							X		X	X						X				X	X	X			11
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA						X																				2
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																	X									1
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA	X	X				X	X	X	X					X			X			X		X	X	X		27
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS																										2
ADENOMA, NOS							X			X							X	X							X	10
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA												X													X	1
PHEOCHROMOCYTOMA																	X									5
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA					X																			X		2
FOLLICULAR-CELL CARCINOMA																										2
C-CELL CARCINOMA																						X				2
PARATHYROID	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	47
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA								X																		5
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROADENOMA																										1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	48
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*
ADENOCARCINOMA, 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
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*
MONOCYTIC LEUKEMIA	X			X																		X				5
SITE UNKNOWN																										
NEURILEMOMA															X											1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
B: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
P: NO NECROPSY PERFORMED

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

HIGH DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	0961	1103	1004	0404	1004	1004	1004	1106	0801	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	0707	1004	0809	1004	1004
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
KERATOACANTHOMA														X											
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
FIBROMA							X			X															
LIPOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS, METASTATIC	X																								
LIPOSARCOMA, METASTATIC																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS	X																								
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																			X						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA			X		X	X	X	X		X	X	X	X	X	X		X	X	X	X			X	X	X
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUCINOUS ADENOCARCINOMA					X																				
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMA, NOS							X	X			X											X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL CARCINOMA													X	X											
PHEOCHROMOCYTOMA						X																		X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA													X												
C-CELL CARCINOMA																	X								
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA												X											X		
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
FIBROADENOMA																									
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
CARCINOMA, NOS										X															
ADENOCARCINOMA, NOS															X										
CYSTADENOCARCINOMA, NOS													X										X		
SARCOMA, NOS																									
BULBOURETHRAL 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
CYSTADENOMA, NOS															X										
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
LIPOSARCOMA																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																X									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEMANGIOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MONOCYTIC LEUKEMIA		X					X										X								

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	104	104	105	105	105	105	105	105	105	121	105	103	105	105	105	105	105	105	079	076	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																						X				1
KERATOACANTHOMA																								X		2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
FIBROMA		X					X																	X		5
LIPOMA		X																								1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SARCOMA, NOS, METASTATIC																										1
LIPOSARCOMA, METASTATIC								X																		1
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE								X																		2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X			X		X	X		37
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUCINOUS ADENOCARCINOMA																								X		2
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ADENOMA, NOS			X		X											X										7
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL CARCINOMA							X																			1
PHEOCHROMOCYTOMA		X	X				X															X				8
THYROID	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA							X							X												2
C-CELL ADENOMA			X																				X			2
C-CELL CARCINOMA										X																3
PARATHYROID	+	-	-	+	+	+	+	+	-	+	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+	41
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA					X															X		X				5
ISLET-CELL CARCINOMA																									X	1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS									X					X												2
FIBROADENOMA					X																			X		2
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X		X	X	X	X		X	X		X	X	X		X				X	X	X	X		X	37
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*
CARCINOMA, NOS																			X							2
ADENOCARCINOMA, NOS																										1
CYSTADENOCARCINOMA, NOS																	X									3
SARCOMA, NOS									X																	1
BULBOURETHRAL 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*
CYSTADENOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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*
LIPOSARCOMA								X																		1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
MESOTHELIOMA, NOS																										1
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*
HEMANGIOSARCOMA												X														1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	X	N	N	N	N	X	N	50*
MONOCYTIC LEUKEMIA																								X		6

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
\- REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X TUMOR INCIDENCE
N NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S ANIMAL MIS-SEXED
B NO TISSUE INFORMATION SUBMITTED
C NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A AUTOLYSIS
M ANIMAL MISSING
B NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	0012	0023	0034	0045	0056	0067	0078	0089	0091	0101	0112	0123	0134	0145	0156	0167	0178	0189	0191	0202	0211	0223	0234	0245
WEEKS ON STUDY	104	104	104	078	104	095	096	096	096	096	096	096	088	101	096	096	092	096	096	096	096	096	096	103
INTEGUMENTARY SYSTEM																								
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA								X																
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RHABDOMYOSARCOMA										X														
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																			X					
ALVEOLAR/BRONCHIOLAR CARCINOMA									X															
C-CELL CARCINOMA, METASTATIC													X											
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE														X										
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS																								
ADENOMA, NOS					X	X	X				X	X	X						X		X	X	X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X																						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA			X																					
C-CELL CARCINOMA												X	X	X							X			
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
PANCREATIC ISLETS	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA						X																		
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																								
CYSTADENOMA, NOS																								
FIBROADENOMA	X					X	X	X				X	X				X						X	X
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA, NOS																								
ADENOMA, NOS																								
REPRODUCTIVE SYSTEM (CONT)																								
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS																								
ADENOMA, NOS																				X				
ADENOCARCINOMA, NOS	X																							
ENDOMETRIAL STROMAL POLYP	X	X		X		X		X												X	X			X
ENDOMETRIAL STROMAL SARCOMA			X																					
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, 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
MONOCYTIC LEUKEMIA																		X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	106	106	091	106	106	106	093	106	106	106	106	106	106	106	100	106	106	106	106	098	098	106	106	106	106	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
SQUAMOUS CELL PAPILLOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
RHABDOMYOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
C-CELL CARCINOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS			X																							1
ADENOMA, NOS				X		X				X					X				X			X			X	18
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA					X				X							X									X	6
C-CELL CARCINOMA																X										4
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	48
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
ADENOCARCINOMA, NOS				X																						1
CYSTADENOMA, NOS							X																			1
FIBROADENOMA			X			X							X		X	X	X					X				16
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																								1
REPRODUCTIVE SYSTEM (CONT)																										
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS					X																					1
ADENOMA, NOS																										1
ADENOCARCINOMA, NOS																					X					2
ENDOMETRIAL STROMAL POLYP	X														X			X			X					12
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS, 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*
MONOCYTIC LEUKEMIA															X											2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	088	105	105	105	105	105	105	105	105	105	096	105	105	105	080	105	091	105	083	081	105	104	103
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SEBACEOUS ADENOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
NEURILEMOMA										X															
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC																									
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
C-CELL CARCINOMA, METASTATIC								X																	
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE									X									X							
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS			X																		X	X			
ADENOMA, NOS				X										X		X				X				X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA											X											X			
PHEOCHROMOCYTOMA																								X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA												X				X								X	
C-CELL CARCINOMA	X							X																	
CYSTADENOMA, NOS																							X		
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROADENOMA		X		X	X	X	X		X		X	X		X						X					X
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP	X								X												X			X	
ENDOMETRIAL STROMAL SARCOMA			X														X								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR																				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
ADENOSQUAMOUS CARCINOMA																									
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
LYMPHOCYTIC LEUKEMIA																			X						
MONOCYTIC LEUKEMIA																					X				
DIAPHRAGM NOS																									
ADENOCARCINOMA, NOS, METASTATIC																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	110	108	094	105	105	105	105	105	094	072	082	105	105	105	105	072	105	105	105	105	105	101	105	105	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																				X						1
SEBACEOUS ADENOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																		X								1
NEURILEMOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC			X																							1
ALVEOLAR/BRONCHIOLAR CARCINOMA														X												1
C-CELL CARCINOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA, NOS														X			X					X	X			3
ADENOMA, NOS																										10
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA		X																X							X	2
PHEOCHROMOCYTOMA																										4
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																		X								1
FOLLICULAR-CELL CARCINOMA							X												X							2
C-CELL *ADENOMA*								X																		4
C-CELL CARCINOMA													X	X												5
CYSTADENOMA, NOS																									X	1
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+		46
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROADENOMA			X	X		X		X												X		X				17
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS			X																						X	3
ENDOMETRIAL STROMAL POLYP	X					X		X							X				X					X		9
ENDOMETRIAL STROMAL SARCOMA																							X			3
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR																										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	50
ADENOSQUAMOUS CARCINOMA																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
LYMPHOCYTIC LEUKEMIA										X																1
MONOCYTIC LEUKEMIA																										2
DIAPHRAGM NOS																										
ADENOCARCINOMA, NOS, METASTATIC			X																							1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
1: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF BENZYL ACETATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	103	104	079	103	104	085	104	104	103	104	104	104	104	104	104	085	104	104	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
CARCINOMA, NOS						X																			
ADENOMA, NOS							X	X				X	X	X	X			X				X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA										X															
GANGLIONEUROMA																									
THYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																	X								
C-CELL ADENOMA									X									X							
C-CELL CARCINOMA											X												X	X	
PARATHYROID	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																		X							
PAPILLARY ADENOCARCINOMA																		X							
FIBROADENOMA						X	X		X		X		X	X	X	X		X		X					
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA, NOS																									
ADENOMA, NOS																									
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS																								X	
ENDOMETRIAL STROMAL POLYP	X				X		X			X		X					X		X					X	
ENDOMETRIAL STROMAL SARCOMA	X																								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
ADENOSQUAMOUS CARCINOMA																									
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, MALIGNANT																									
MONOCYTIC LEUKEMIA				X																					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	088	115	105	105	105	105	105	105	105	105	105	098	105	105	091	094	080	070	105	105	105	091	096	105	
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																									1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE					X																				1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA, NOS																									1
ADENOMA, NOS		X	X		X							X		X											14
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
GANGLIONEUROMA		X																							1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																									1
C-CELL ADENOMA		X										X													4
C-CELL CARCINOMA					X																				4
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																							X		1
PAPILLARY ADENOCARCINOMA																									1
FIBROADENOMA							X		X	X						X				X	X				16
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	50M
CARCINOMA, NOS									X					X											2
ADENOMA, NOS															X					X	X				5
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA, NOS																									1
ENDOMETRIAL STROMAL POLYP	X			X			X	X		X	X	X						X					X		18
ENDOMETRIAL STROMAL SARCOMA																		X						X	5
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	50M
ADENOSQUAMOUS CARCINOMA																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	50M
MESOTHELIOMA, MALIGNANT																X									1
MONOCYTIC LEUKEMIA																									1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX B
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
FIBROSARCOMA		2 (4%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	4 (8%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	7 (14%)	4 (8%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (10%)	3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS		2 (4%)	1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	3 (6%)	2 (4%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	
LYMPHOCYTIC LEUKEMIA		2 (4%)	
#SPLEEN	(50)	(49)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#MESENTERIC L. NODE	(50)	(49)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#PEYERS PATCH	(48)	(48)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
CIRCULATORY SYSTEM			
*SKIN	(50)	(49)	(50)
HEMANGIOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
*SUBCUT TISSUE	(50)	(49)	(50)
HEMANGIOMA		1 (2%)	
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA	3 (6%)	2 (4%)	1 (2%)
#LIVER	(50)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
NEOPLASM, NOS			1 (2%)
HEPATOCELLULAR ADENOMA		5 (10%)	13 (26%)
HEPATOCELLULAR CARCINOMA	10 (20%)	14 (29%)	12 (24%)
#GLANDULAR STOMACH	(49)	(48)	(49)
CARCINOMA, NOS		1 (2%)	
#FORESTOMACH	(49)	(48)	(49)
SQUAMOUS CELL PAPILLOMA	3 (6%)	3 (6%)	9 (18%)
SQUAMOUS CELL CARCINOMA	1 (2%)	1 (2%)	2 (4%)
#SMALL INTESTINE	(48)	(48)	(47)
MUCINOUS ADENOCARCINOMA	1 (2%)		
#JEJUNUM	(48)	(48)	(47)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
TUBULAR-CELL ADENOMA			1 (2%)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(46)
CARCINOMA, NOS	1 (2%)		
#ADRENAL	(50)	(47)	(49)
PHEOCHROMOCYTOMA		2 (4%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL MEDULLA	(50)	(47)	(49)
GANGLIONEUROMA			1 (2%)
#THYROID	(49)	(49)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)	3 (6%)	4 (9%)
#PANCREATIC ISLETS	(50)	(49)	(49)
ISLET-CELL ADENOMA		1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
#TESTIS	(49)	(49)	(50)
INTERSTITIAL-CELL TUMOR	1 (2%)		2 (4%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS	2 (4%)		3 (6%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
SARCOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	7	6	7
MORIBUND SACRIFICE	5	9	3
SCHEDULED SACRIFICE	5		
TERMINAL SACRIFICE	33	32	39
ACCIDENTALLY KILLED, NOS		2	1
ANIMAL MISSING		1	
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	32	35	36
TOTAL PRIMARY TUMORS	43	54	63
TOTAL ANIMALS WITH BENIGN TUMORS	12	15	24
TOTAL BENIGN TUMORS	14	20	41
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	28	19
TOTAL MALIGNANT TUMORS	29	34	21
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	4	3
TOTAL SECONDARY TUMORS	1	4	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	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			
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS			2 (4%)
FIBROSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	2 (4%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE	4 (8%)	2 (4%)	3 (6%)
UNDIFFERENTIATED LEUKEMIA	1 (2%)	1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA		2 (4%)	
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA			6 (12%)

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEPATOCELLULAR CARCINOMA	1 (2%)		4 (8%)
MIXED HEPATO/CHOLANGIO CARCINOMA		1 (2%)	
#FORESTOMACH	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA			4 (8%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(46)	(46)
CARCINOMA, NOS		1 (2%)	
ADENOMA, NOS	3 (6%)	4 (9%)	3 (7%)
#ADRENAL	(50)	(50)	(47)
CORTICAL ADENOMA	1 (2%)		
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA			2 (4%)
#THYROID	(47)	(50)	(49)
FOLLICULAR-CELL ADENOMA	3 (6%)	2 (4%)	2 (4%)
#PANCREATIC ISLETS	(49)	(50)	(48)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		2 (4%)	
MIXED TUMOR, MALIGNANT		1 (2%)	
#UTERUS	(50)	(50)	(50)
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	1 (2%)	
NEURILEMOMA, MALIGNANT	1 (2%)	1 (2%)	
#CERVIX UTERI	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
NEURILEMOMA, MALIGNANT		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#UTERUS/MYOMETRIUM	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
#OVARY	(50)	(50)	(45)
TERATOMA, NOS			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC		1 (2%)	
MIXED HEPATO/CHOLANGIOCA, METAST		1 (2%)	
NEURILEMOMA, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	20	13	8
MORIBUND SACRIFICE	15	15	11
SCHEDULED SACRIFICE	5		
TERMINAL SACRIFICE	10	18	30
ACCIDENTALLY KILLED, NOS		4	1

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	26	25
TOTAL PRIMARY TUMORS	18	34	34
TOTAL ANIMALS WITH BENIGN TUMORS	6	9	13
TOTAL BENIGN TUMORS	8	10	17
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	19	15
TOTAL MALIGNANT TUMORS	10	24	16
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	
TOTAL SECONDARY TUMORS	1	2	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1
TOTAL UNCERTAIN TUMORS			1

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	029	096	105	105	105	105	029	029	105	105	088	105	105	105	105
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS																									
ALVEOLAR/BRONCHIOLAR ADENOMA					X			X		X														X	
ALVEOLAR/BRONCHIOLAR CARCINOMA																									X
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA							X				X														
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA												X		X					X		X		X		X
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	N	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA									X											X					
SQUAMOUS CELL CARCINOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+
MUCINOUS ADENOCARCINOMA								X																	
MALIGNANT LYMPHOMA, MIXED TYPE																								X	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+
CARCINOMA, NOS																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	-	+	+	+	-	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
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						X																		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
SARCOMA, 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
MALIG.LYMPHOMA, LYMPHOCYTIC TYP	X																				X				
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	115	105	105	105	105	033	066	051	105	106	036	088	106	005	106	072	106	061	106	106	106	106	084	106	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METAS									X																	1
ALVEOLAR/BRONCHIOLAR ADENOMA	X	X														X										7
ALVEOLAR/BRONCHIOLAR CARCINOMA										X	X											X	X			5
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																		X								3
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA			X							X										X						10
HEMANGIOSARCOMA													X					X								2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA	X																									3
SQUAMOUS CELL CARCINOMA																	X									1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MUCINOUS ADENOCARCINOMA																										1
MALIGNANT LYMPHOMA, MIXED TYPE																										1
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
CARCINOMA, NOS																				X						1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA									X																	1
PARATHYROID	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	-	-	-	-	+	-	36
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	+	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
INTERSTITIAL-CELL TUMOR														X												1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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																										2
BODY CAVITIES																										
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
SARCOMA, NOS							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*
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																					X					3
MALIGNANT LYMPHOMA, MIXED TYPE														X												1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	009	048	105	105	105	097	072	105	118	105	068	088	097	105	105	105	105	105	099	052	105	105	090	105	094
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																									
HEMANGIOMA																		X							
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS					X						X														
ALVEOLAR/BRONCHIOLAR ADENOMA											X		X									X			
ALVEOLAR/BRONCHIOLAR CARCINOMA															X			X							
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																			X	X					
MALIGNANT LYMPHOMA, MIXED TYPE			X																						
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X									X													X	
HEPATOCELLULAR CARCINOMA					X	X					X					X						X	X		
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS																									
SQUAMOUS CELL PAPILLOMA																				X		X			
SQUAMOUS CELL CARCINOMA																									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																				X					
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+
ADRENAL	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PHEOCHROMOCYTOMA								X																	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																				X					
PARATHYROID	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	N	N	N	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
MALIGNANT LYMPHOMA, NOS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																									X
MALIG.LYMPHOMA, HISTIOCYTIC TYP							X																		
MALIGNANT LYMPHOMA, MIXED TYPE												X	X												
LYMPHOCYTIC LEUKEMIA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: *NO NECROPSY PERFORMED*

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 30	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 01	04 11	04 42	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	11 05	03 36	01 51	01 51	01 51	01 51	08 81	01 51	01 51	01 51	01 51	01 51	01 51	01 51	04 10	09 01	01 51	01 51	08 91	01 51	09 11	01 51	01 51	01 51	01 50	
INTEGUMENTARY SYSTEM																										
SKIN	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
HEMANGIOMA																									X	1
SUBCUTANEOUS TISSUE	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
FIBROSARCOMA														X							X					2
HEMANGIOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR CARCINOMA, METAS									X													X				4
ALVEOLAR/BRONCHIOLAR ADENOMA							X																			4
ALVEOLAR/BRONCHIOLAR CARCINOMA																								X		3
TRACHEA	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOSARCOMA																										2
MALIGNANT LYMPHOMA, MIXED TYPE																										1
LYMPH NODES	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	M	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
HEART	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA					X																					5
HEPATOCELLULAR CARCINOMA								X	X			X		X		X			X			X	X			14
HEMANGIOSARCOMA												X														1
BILE DUCT	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	+	M	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	49*
PANCREAS	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	M	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA, NOS																							X			1
SQUAMOUS CELL PAPILLOMA								X																		3
SQUAMOUS CELL CARCINOMA																			X							1
SMALL INTESTINE	+	M	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOCARCINOMA, NOS																										1
LARGE INTESTINE	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	●	-	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	M	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
ADRENAL	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PHEOCHROMOCYTOMA																								X		2
THYROID	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA											X			X												3
PARATHYROID	+	M	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
PANCREATIC ISLETS	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA													X													1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	M	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
TESTIS	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
MALIGNANT LYMPHOMA, NOS							X								X											2
MALIG.LYMPHOMA, LYMPHOCYTIC TYP				X												X										2
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										1
MALIGNANT LYMPHOMA, MIXED TYPE																										1
LYMPHOCYTIC LEUKEMIA																										2

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	094	105	105	105	105	105	105	051	105	098	105	105	105	105	105	105	072	105	088	105	105	105	105	105	105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METAS																			X							1
ALVEOLAR/BRONCHIOLAR ADENOMA									X						X	X		X								6
ALVEOLAR/BRONCHIOLAR CARCINOMA																		X								2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIGNANT LYMPHOMA, MIXED TYPE																										1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASM, NOS																										1
HEPATOCELLULAR ADENOMA		X		X			X		X						X	X		X		X			X		X	13
HEPATOCELLULAR CARCINOMA	X									X	X					X	X		X							12
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
SQUAMOUS CELL PAPILLOMA					X								X		X	X						X				9
SQUAMOUS CELL CARCINOMA									X																	2
SMALL INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA															X											1
TUBULAR-CELL ADENOCARCINOMA		X																								1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	46
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GANGLIONEUROMA				X																						1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	47
FOLLICULAR-CELL ADENOMA		X		X																						4
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	-	+	44
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																							X			2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR		X																					X			2
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
ADENOMA, NOS				X										X												3
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*
HEPATOCELLULAR CARCINOMA, METAS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
HEPATOCELLULAR CARCINOMA, METAS																										1
MALIGNANT LYMPHOMA, NOS																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYP						X																				1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	094	094	094	104	104	104	103	088	104	104	064	094	094	094	094	094	094	088	094	093	094	094	123	094
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METAS																									
ALVEOLAR/BRONCHIOLAR ADENOMA				X												X					X				
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																				X					
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, MIXED TYPE																X									
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASM, NOS		X																							
HEPATOCELLULAR ADENOMA	X					X		X				X					X								X
HEPATOCELLULAR CARCINOMA																	X		X	X					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA													X	X		X							X		
SQUAMOUS CELL CARCINOMA															X										
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																									
TUBULAR-CELL ADENOCARCINOMA																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
GANGLIONEUROMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA				X																X					
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA	X																								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	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																							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
HEPATOCELLULAR CARCINOMA, METAS																			X						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEPATOCELLULAR CARCINOMA, METAS								X																	
MALIGNANT LYMPHOMA, NOS																					X				
MALIG.LYMPHOMA, LYMPHOCYTIC TYP																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

VEHICLE CONTROL

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	a 9 1	0 9	0 7 8	1 0 4	1 0 4	1 0 4	1 0 4	5 9 1	6 7 6	6 7 9	6 0 4	6 0 5	6 2 1	6 2 1	6 2 1	6 3	d 1 0 5	d 1 0 5	5 7 0	d 8 7	d 6 3	6 6 6	6 6 8	6 5 5	6 0 7	d 8 3	0 8 5
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN HEMANGI05ARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY **GLAND**	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER **HEPATOCELLULAR** CARCINOHA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	*				+	+	+		+	+	+					+	+		+	+	+	+	+	+	
ENDOCRINE SYSTEM																									
PITUITARY ADENOMA, NOS	+	-	+	+	+ X	+ X	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADRENAL CORTICAL ADENOMA	+	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID **FOLLICULAR-CELL** ADENOMA	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+ X	+	+	-	+	+	+	+	+	+
P RATHYRO D	-	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS ENDOMETRIAL STROMAL SARCOMA NEURILEMOMA, MALIGNANT	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NEURILEMOMA, METASTATIC																									
MALIG LYMPHOMA, LYMPHOCYTIC TYP																									
MALIGNANT LYMPHOMA, MIXED TYPE				X				X																	
UNDIFFERENTIATED LEUKEMIA			X																						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 30	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 42	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 00	TOTAL
WEEKS ON STUDY	10 05	10 05	07 09	09 01	07 02	10 06	08 03	08 10	09 11	08 05	01 16	03 08	10 06	09 16	09 01	06 07	10 16	10 16	10 16	08 08	10 11	09 04	08 07	09 16	10 06	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN HEMANGIOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
THYMUS	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
LIVER *HEPATOCELLULAR CARCINOMA*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	50 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	N	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	N	+	+	N	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+	39
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	48 3
ADRENAL CORTICAL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
THYROID FOLLICULAR-CELL ADENOMA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	-	+	+	+	+	+	+	+	47 3
PARATHYROID	-	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+	-	+	37
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
UTERUS ENDOMETRIAL STROMAL SARCOMA NEURILEMOMA, MALIGNANT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	50 1 1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS NEURILEMOMA, METASTATIC MALIG.LYMPHOMA, LYMPHOCYTIC TYP MALIGNANT LYMPHOMA, MIXED TYPE UNDIFFERENTIATED LEUKEMIA	N	N	N	N	N	N	N	N	N	N	N	N	N X	N X	N	N	N X	N X	N	N	N	N	N	N	N	50M 1 1 4 1

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: *REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY*
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

LOW DOSE

ANIMAL NUMBER	0011	0021	0031	0041	0051	0061	0071	0081	0091	0101	0111	0121	0131	0141	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251
WEEKS ON STUDY	105	105	105	041	055	072	074	074	091	105	072	097	079	095	105	069	073	068	095	100	105	103	105	095	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																	X								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA												X						X							
ALVEOLAR/BRONCHIOLAR CARCINOMA													X												
TRACHEA	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																X									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MIXED HEPATO/CHOLANGIO CARCINOM																									
HEMANGIOSARCOMA																X									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
CARCINOMA, NOS																									
ADENOMA, NOS	X																					X			
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL CARCINOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																						X			
PARATHYROID	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA												X													
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N
ADENOCARCINOMA, NOS						X				X															
MIXED TUMOR, MALIGNANT																							X		
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS														X											
LEIOMYOSARCOMA														X											
ENDOMETRIAL STROMAL POLYP															X										
ENDOMETRIAL STROMAL SARCOMA																									
NEURILEMOMA, MALIGNANT			X						X																
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS, METASTATIC						X																			
MIXED HEPATO/CHOLANGIOCA, METAS																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYP	X																								
MALIG.LYMPHOMA, HISTIOCYTIC TYP													X									X			
MALIGNANT LYMPHOMA, MIXED TYPE																		X							
UNDIFFERENTIATED LEUKEMIA																									
LYMPHOCYTIC LEUKEMIA																				X					

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	095	085	087	082	038	000	000	105	105	105	105	076	000	105	056	051	051	050	058	058	099	095	098	072	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																										2
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	50
MIXED HEPATO/CHOLANGIO CARCINOM																										1
HEMANGIOSARCOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	46
CARCINOMA, NOS												X														1
ADENOMA, NOS								X		X																4
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL CARCINOMA																						X				1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA										X																2
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	45
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
ADENOCARCINOMA, NOS																										2
MIXED TUMOR, MALIGNANT																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
LEIOMYOSARCOMA																										1
ENDOMETRIAL STROMAL POLYP																										1
ENDOMETRIAL STROMAL SARCOMA																										1
NEURILEMOMA, MALIGNANT																									X	2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOCARCINOMA, NOS, METASTATIC																										1
MIXED HEPATO/CHOLANGIOCA, METAS																						X				1
MALIG.LYMPHOMA, LYMPHOCYTIC TYP											X															2
MALIG.LYMPHOMA, HISTIOCYTIC TYP																										2
MALIGNANT LYMPHOMA, MIXED TYPE								X																		2
UNDIFFERENTIATED LEUKEMIA																									X	1
LYMPHOCYTIC LEUKEMIA												X														2

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF BENZYL ACETATE

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	021	022	023	024	025
WEEKS ON STUDY	073	104	104	062	057	091	095	104	104	096	087	104	104	104	080	085	080	076	087	071	104	104	104	104
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS		X																						
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR CARCINOMA																								
TRACHEA	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X							X		X								X					
HEPATOCELLULAR CARCINOMA			X																		X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																								
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																								
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
PHEOCHROMOCYTOMA							X																	
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																X								
PARATHYROID	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																								
OVARY	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TERATOMA, NOS																								
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
MALIG.LYMPHOMA, LYMPHOCYTIC TYP							X							X										
MALIG.LYMPHOMA, HISTIOCYTIC TYP																								
MALIGNANT LYMPHOMA, MIXED TYPE									X															
UNDIFFERENTIATED LEUKEMIA																		X						

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 30	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 42	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	07 00	06 08	04 01	02 00	05 15	05 15	05 15	05 15	05 15	05 15	05 15	05 15	05 15	05 15	05 15	07 20	05 15	09 15	05 15	05 15	08 08	02 00	05 15	05 15	05 15	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS															X											2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR CARCINOMA																									X	1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																			X					X		6
HEPATOCELLULAR CARCINOMA					X																X					4
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SQUAMOUS CELL PAPILLOMA						X				X	X													X		4
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ADENOMA, NOS						X					X							X								3
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	47
PHEOCHROMOCYTOMA							X																			2
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL ADENOMA																		X								2
PARATHYROID	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	45
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	N	+	+	+	50M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOSARCOMA						X																				1
OVARY	+	+	+	+	+	+	-	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	45
TERATOMA, NOS																					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	N	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYP													X													2
MALIG.LYMPHOMA, HISTIOCYTIC TYP	X																									2
MALIGNANT LYMPHOMA, MIXED TYPE																			X						X	3
UNDIFFERENTIATED LEUKEMIA																										1

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

APPENDIX C
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	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%)		1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
HYPERKERATOSIS	5 (10%)	4 (8%)	4 (8%)
ACANTHOSIS		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)	1 (2%)	1 (2%)
HEMORRHAGE		1 (2%)	
HEMORRHAGE, CHRONIC			1 (2%)
STEATITIS		2 (4%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
FIBROSIS	1 (2%)		1 (2%)
FIBROSIS, FOCAL			1 (2%)
METAPLASIA, OSSEOUS			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(48)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
PNEUMONIA, ASPIRATION			1 (2%)
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, ADENOMATOUS		2 (4%)	
#LUNG/ALVEOLI	(50)	(50)	(48)
HISTIOCYTOSIS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(47)	(50)
MYELOFIBROSIS			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(50)	(50)	(49)
ANGIECTASIS		1 (2%)	
HEMATOPOIESIS	2 (4%)		2 (4%)
#MANDIBULAR L. NODE	(50)	(50)	(50)
CYST, NOS	1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)
#INGUINAL LYMPH NODE	(50)	(50)	(50)
HEMORRHAGIC CYST	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#AURICULAR APPENDAGE	(50)	(50)	(50)
THROMBUS, MURAL			1 (2%)
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	34 (68%)	31 (62%)	37 (74%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
CHOLANGIOFIBROSIS	4 (8%)	4 (8%)	1 (2%)
NECROSIS, CYTODEGENERATIVE	1 (2%)		
NECROSIS, COAGULATIVE			1 (2%)
CYTOPLASMIC VACUOLIZATION	7 (14%)	10 (20%)	6 (12%)
FOCAL CELLULAR CHANGE			1 (2%)
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(49)	(50)	(50)
NECROSIS, COAGULATIVE			1 (2%)
#BILE DUCT	(49)	(50)	(50)
DILATATION, NOS	1 (2%)		
HYPERPLASIA, NOS	26 (53%)	15 (30%)	7 (14%)
#PANCREATIC ACINUS	(50)	(50)	(49)
FOCAL CELLULAR CHANGE	4 (8%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	1 (2%)		1 (2%)
ATROPHY, FOCAL	24 (48%)	21 (42%)	13 (27%)
HYPERPLASIA, NOS	2 (4%)	7 (14%)	
HYPERPLASIA, FOCAL	35 (70%)	27 (54%)	36 (73%)
#STOMACH	(50)	(50)	(48)
HYPERPLASIA, EPITHELIAL			1 (2%)
#GASTRIC MUCOSA	(50)	(50)	(48)
ULCER, NOS	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, BASAL CELL			1 (2%)
#GASTRIC SUBMUCOSA	(50)	(50)	(48)
EDEMA, NOS	1 (2%)		1 (2%)
#SMALL INTESTINE	(49)	(49)	(49)
INFLAMMATION, CHRONIC			1 (2%)
DIVERTICULITIS			1 (2%)
#COLON	(50)	(50)	(49)
PARASITISM	1 (2%)		
*RECTUM	(50)	(50)	(50)
POLYP, INFLAMMATORY			1 (2%)
*RECTAL SUBMUCOSA	(50)	(50)	(50)
EDEMA, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
INFLAMMATION, CHRONIC	20 (40%)	6 (12%)	22 (44%)
INFARCT, ACUTE			1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
DILATATION, NOS	1 (2%)		
DEGENERATION, NOS	1 (2%)		
#URINARY BLADDER	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(50)	(49)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, FOCAL	1 (2%)		
ANGIECTASIS	3 (6%)	4 (8%)	2 (4%)
#ADRENAL	(50)	(50)	(50)
ACCESSORY STRUCTURE		1 (2%)	
ANGIECTASIS	1 (2%)	4 (8%)	4 (8%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	2 (4%)	3 (6%)	3 (6%)
HYPERPLASIA, NOS			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
#THYROID	(50)	(50)	(49)
THYROGLOSSAL DUCT CYST		2 (4%)	
CYSTIC FOLLICLES	3 (6%)		
DEGENERATION, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	7 (14%)	9 (18%)	1 (2%)
#THYROID FOLLICLE	(50)	(50)	(49)
HYPERPLASIA, CYSTIC	2 (4%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	10 (20%)	2 (4%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE		2 (4%)	2 (4%)
#PROSTATE	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION, SUPPURATIVE	5 (10%)	5 (10%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, GRANULOMATOUS		1 (2%)	

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, EPITHELIAL		1 (2%)	
*SEMINAL VESICLE	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
#TESTIS	(50)	(50)	(50)
ATROPHY, NOS	3 (6%)		1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	4 (8%)	2 (4%)	17 (34%)
NERVOUS SYSTEM			
#CEREBRUM	(50)	(50)	(50)
GLIOSIS	1 (2%)		
#BRAIN	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
#CEREBELLUM	(50)	(50)	(50)
STATUS SPONGIOSUS		1 (2%)	2 (4%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY	1 (2%)		20 (40%)
PHTHISIS BULBI			2 (4%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
CATARACT			13 (26%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
STEATITIS	1 (2%)	6 (12%)	1 (2%)
NECROSIS, FAT	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
FOOT			
HYPERKERATOSIS	1		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ACANTHOSIS	1		
ADIPOSE TISSUE			
STEATITIS		1	
OMENTUM			
NECROSIS, FAT	1	1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
FIBROSIS			1 (2%)
HYPERKERATOSIS	7 (14%)	8 (16%)	20 (40%)
ACANTHOSIS	4 (8%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	1 (2%)
HYPERPLASIA, ADENOMATOUS		1 (2%)	2 (4%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		3 (6%)
#LUNG/ALVEOLI	(50)	(50)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(50)	(50)
CONGESTION, NOS			1 (2%)
ATROPHY, NOS			1 (2%)
#SPLEEN	(49)	(50)	(50)
HEMATOPOIESIS	2 (4%)	4 (8%)	3 (6%)
#MANDIBULAR L. NODE	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#ILIAC LYMPH NODE	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#INGUINAL LYMPH NODE	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		2 (4%)	
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	17 (34%)	12 (24%)	19 (38%)
INFLAMMATION, CHRONIC FOCAL		2 (4%)	1 (2%)
#ADRENAL CORTEX	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
NECROSIS, COAGULATIVE		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	2 (4%)	2 (4%)
BASOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
FOCAL CELLULAR CHANGE	3 (6%)	2 (4%)	1 (2%)
ANGIECTASIS		3 (6%)	2 (4%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS		3 (6%)	1 (2%)
#PANCREAS	(49)	(50)	(49)
ATROPHY, NOS		1 (2%)	1 (2%)
#STOMACH	(49)	(49)	(49)
EPIDERMAL INCLUSION CYST			1 (2%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, NECROTIZING		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
#GASTRIC MUCOSA	(49)	(49)	(49)
ULCER, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#GASTRIC SUBMUCOSA	(49)	(49)	(49)
EDEMA, NOS			2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	4 (8%)
#KIDNEY/TUBULE	(50)	(50)	(50)
PIGMENTATION, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(50)	(49)	(48)
CYST, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		1 (2%)
ANGIECTASIS	8 (16%)	11 (22%)	5 (10%)
#ADRENAL	(50)	(50)	(50)
ACCESSORY STRUCTURE		1 (2%)	
CYST, NOS			1 (2%)
NECROSIS, ISCHEMIC			1 (2%)
CYTOPLASMIC VACUOLIZATION	3 (6%)		
ANGIECTASIS	1 (2%)	3 (6%)	3 (6%)
#ADRENAL CORTEX	(50)	(50)	(50)
CYST, NOS	1 (2%)		
DEGENERATION, LIPOID	1 (2%)		
CYTOPLASMIC VACUOLIZATION	8 (16%)	3 (6%)	3 (6%)
HYPERPLASIA, NODULAR		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#THYROID	(50)	(50)	(49)
CYSTIC FOLLICLES	2 (4%)		
HYPERPLASIA, C-CELL	7 (14%)	6 (12%)	6 (12%)
#THYROID FOLLICLE	(50)	(50)	(49)
HYPERPLASIA, CYSTIC		1 (2%)	3 (6%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	16 (32%)	16 (32%)	11 (22%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC		2 (4%)	2 (4%)
*MAMMARY LOBULE	(50)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	3 (6%)	2 (4%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS	2 (4%)		
INFLAMMATION, CHRONIC	1 (2%)		
*CLITORAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE		2 (4%)	1 (2%)
INFLAMMATION CHRONIC SUPPURATIVE			1 (2%)
*VAGINA	(50)	(50)	(50)
POLYP, INFLAMMATORY	1 (2%)		
#UTERUS	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
PYOMETRA		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
CYST, NOS	2 (4%)	2 (4%)	
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, CYSTIC	7 (14%)	1 (2%)	2 (4%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CEREBELLUM	(50)	(50)	(50)
STATUS SPONGIOSUS		6 (12%)	1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY		18 (36%)	1 (2%)
PHTHISIS BULBI			2 (4%)
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
MINERALIZATION		3 (6%)	
CATARACT		3 (6%)	
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
OSTEOSCLEROSIS		1 (2%)	
*FEMUR	(50)	(50)	(50)
OSTEOSCLEROSIS			1 (2%)
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
STEATITIS		2 (4%)	1 (2%)
NECROSIS, FAT	2 (4%)	1 (2%)	
ALL OTHER SYSTEMS			
OMENTUM			
HEMORRHAGE		1	
STEATITIS		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1		

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

APPENDIX D
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
ULCER, FOCAL	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	3 (6%)	1 (2%)	1 (2%)
FIBROSIS	2 (4%)	1 (2%)	
FIBROSIS, FOCAL			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)
EDEMA, NOS			2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, GRANULOMATOUS	1 (2%)		
INFLAMMATION, PYOGRANULOMATOUS	2 (4%)		
ANGIECTASIS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(49)	(50)
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)		
#LUNG	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, INTERSTITIAL	1 (2%)		
PNEUMONIA, ASPIRATION		1 (2%)	
INFLAMMATION, GRANULOMATOUS			2 (4%)
GRANULOMA, NOS			1 (2%)
INFLAMMATION GRANULOMATOUS FOCAL	2 (4%)		2 (4%)
CHOLESTEROL DEPOSIT			5 (10%)
HYPERPLASIA, ADENOMATOUS	11 (22%)	13 (27%)	15 (30%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
#LUNG/ALVEOLI	(50)	(49)	(50)
HISTIOCYTOSIS	1 (2%)		1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)
*BLOOD	(50)	(49)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
#BONE MARROW	(50)	(49)	(50)
ATROPHY, NOS		1 (2%)	
MYELOFIBROSIS		1 (2%)	
HYPERPLASIA, GRANULOCYTIC		1 (2%)	
#SPLEEN	(50)	(49)	(49)
ATROPHY, NOS			1 (2%)
ANGIECTASIS		2 (4%)	
HYPERPLASIA, LYMPHOID	2 (4%)		2 (4%)
HEMATOPOIESIS	3 (6%)	3 (6%)	1 (2%)
#MEDIASTINAL L.NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(50)	(49)	(50)
ANGIECTASIS	2 (4%)	2 (4%)	5 (10%)
HYPERPLASIA, LYMPHOID	5 (10%)		1 (2%)
HEMATOPOIESIS		1 (2%)	1 (2%)
#RENAL LYMPH NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	2 (4%)		
#INGUINAL LYMPH NODE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)	
#LUNG/BRONCHIOLE	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#LIVER	(50)	(49)	(50)
MYELOPOIESIS	1 (2%)		
#PEYERS PATCH	(48)	(48)	(47)
HYPERPLASIA, LYMPHOID	2 (4%)		
#KIDNEY	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#U.BLADDER/SUBMUCOSA	(48)	(48)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#THYMUS	(49)	(48)	(49)
CYST, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#LIVER	(50)	(49)	(50)
THROMBOSIS, NOS			2 (4%)
#HEPATIC SINUSOID	(50)	(49)	(50)
DISTENTION	1 (2%)		
#PANCREAS	(50)	(49)	(49)
PERIARTERITIS			1 (2%)
#THYROID	(49)	(49)	(47)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC			2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, NOS			1 (2%)
NECROSIS, COAGULATIVE	5 (10%)	4 (8%)	3 (6%)
PIGMENTATION, NOS			1 (2%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	
FOCAL CELLULAR CHANGE	2 (4%)	1 (2%)	1 (2%)
EOSINOPHILIC CYTO CHANGE	1 (2%)		
CYTOLOGIC ALTERATION, NOS			1 (2%)
ATROPHY, NOS		1 (2%)	
ATROPHY, FOCAL			1 (2%)
ANGIECTASIS	1 (2%)	3 (6%)	2 (4%)
#LIVER/CENTRILOBULAR	(50)	(49)	(50)
NECROSIS, COAGULATIVE		1 (2%)	
#PANCREAS	(50)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#STOMACH	(49)	(48)	(49)
ULCER, FOCAL		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#GASTRIC SUBMUCOSA	(49)	(48)	(49)
INFLAMMATION, SUPPURATIVE			1 (2%)
#FORESTOMACH	(49)	(48)	(49)
CYST, NOS	1 (2%)	2 (4%)	7 (14%)
ULCER, NOS		1 (2%)	3 (6%)
INFLAMMATION, SUPPURATIVE	2 (4%)		2 (4%)
EROSION			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)	7 (15%)	22 (45%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)
INFARCT, FOCAL			1 (2%)
INFARCT, HEALED			3 (6%)
#KIDNEY/PELVIS	(50)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
#URINARY BLADDER	(48)	(48)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(46)
HYPERPLASIA, FOCAL	1 (2%)		
ANGIECTASIS			1 (2%)
#ADRENAL/CAPSULE	(50)	(47)	(49)
HYPERPLASIA, NOS	1 (2%)		
#ADRENAL MEDULLA	(50)	(47)	(49)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(49)	(49)	(47)
FOLLICULAR CYST, NOS	1 (2%)		2 (4%)
DEGENERATION, CYSTIC	1 (2%)	3 (6%)	
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	1 (2%)	1 (2%)
#PANCREATIC ISLETS	(50)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(49)	(50)
CYSTIC DUCTS	7 (14%)	10 (20%)	4 (8%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE	2 (4%)		1 (2%)
ABSCESS, CHRONIC		1 (2%)	
#PROSTATE	(49)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
#TESTIS	(49)	(49)	(50)
MINERALIZATION	1 (2%)		
ATROPHY, NOS	1 (2%)		
*EPIDIDYMIS	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS			2 (4%)
INFLAMMATION GRANULOMATOUS FOCAL	1 (2%)		
CHOLESTEROL DEPOSIT			1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(49)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(50)	(49)	(50)
NECROSIS, FAT	1 (2%)		1 (2%)

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

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
DIAPHRAGM			
INFLAMMATION, CHRONIC FOCAL	1		
OMENTUM			
NECROSIS, FAT	1		
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	4	2	2
ANIMAL MISSING/NO NECROPSY		1	

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

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED BENZYL ACETATE IN CORN OIL BY GAVAGE

	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			
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		
ANGIECTASIS		1 (2%)	
RESPIRATORY SYSTEM			
*NASAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		1 (2%)	
#LUNG/BRONCHIOLE	(49)	(50)	(50)
EDEMA, NOS	1 (2%)		
#LUNG	(49)	(50)	(50)
EMPHYSEMA, ALVEOLAR			1 (2%)
HEMORRHAGE			1 (2%)
INFLAMMATION, INTERSTITIAL		1 (2%)	
BRONCHOPNEUMONIA, ACUTE	1 (2%)		
INFLAMMATION, GRANULOMATOUS	1 (2%)		
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
CHOLESTEROL DEPOSIT	1 (2%)		
HYPERPLASIA, ADENOMATOUS	9 (18%)	4 (8%)	12 (24%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
#LUNG/ALVEOLI	(49)	(50)	(50)
HISTIOCYTOSIS			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
HEMATOPOIESIS	20 (40%)	12 (24%)	3 (6%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)	
HEMATOPOIESIS	2 (4%)		4 (8%)
*MESENTERY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#PERIRENAL TISSUE	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	
#ADRENAL	(50)	(50)	(47)
HEMATOPOIESIS		1 (2%)	
#THYMIC LYMPHOCYTES	(49)	(49)	(49)
NECROSIS, NOS			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#SPLEEN	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#ILIAC LYMPH NODE	(49)	(50)	(49)
LYMPHANGIECTASIS			1 (2%)
#LUNG	(49)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
#HEART	(49)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PULMONARY ARTERY	(50)	(50)	(50)
EDEMA, NOS	1 (2%)		
#KIDNEY	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#BONE MARROW	(50)	(49)	(48)
NECROSIS, FOCAL		1 (2%)	
FIBROUS OSTEODYSTROPHY			1 (2%)
MYELOFIBROSIS	2 (4%)	1 (2%)	2 (4%)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
HYPERPLASIA, GRANULOCYTIC	1 (2%)	1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(50)
ATROPHY, NOS			1 (2%)
ANGIECTASIS		1 (2%)	
HYPERPLASIA, LYMPHOID			3 (6%)
HEMATOPOIESIS	5 (10%)	4 (8%)	7 (14%)
#SPLENIC CAPSULE	(50)	(50)	(50)
FIBROSIS		1 (2%)	
#LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	3 (6%)	1 (2%)	2 (4%)
#BRONCHIAL LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MEDIASTINAL L.NODE	(49)	(50)	(49)
ABSCESS, NOS	1 (2%)	1 (2%)	
#LUMBAR LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	5 (10%)	3 (6%)	1 (2%)
#ILIAC LYMPH NODE	(49)	(50)	(49)
HYPERPLASIA, LYMPHOID	2 (4%)	3 (6%)	
#LUNG	(49)	(50)	(50)
LEUKOSTASIS		1 (2%)	
LEUKOCYTOSIS, NOS	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
*PULMONARY ARTERY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#LIVER	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		2 (4%)	
ABSCESS, CHRONIC			1 (2%)
NECROSIS, COAGULATIVE	1 (2%)	1 (2%)	
NUCLEAR-SIZE ALTERATION			1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
FOCAL CELLULAR CHANGE			2 (4%)
ANGIECTASIS			1 (2%)
#BILE DUCT	(50)	(50)	(50)
CYST, NOS		1 (2%)	
#PANCREATIC ACINUS	(49)	(50)	(48)
ATROPHY, NOS			1 (2%)
#GASTRIC MUCOSA	(50)	(50)	(48)
ULCER, NOS		1 (2%)	
#GLANDULAR STOMACH	(50)	(50)	(48)
METAPLASIA, SQUAMOUS	1 (2%)		
#FORESTOMACH	(50)	(50)	(48)
CYST, NOS		1 (2%)	7 (15%)
MULTIPLE CYSTS			1 (2%)
ULCER, NOS			2 (4%)
INFLAMMATION, SUPPURATIVE		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)	6 (12%)	17 (35%)
HYPERKERATOSIS			3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
PYELONEPHRITIS, NOS		1 (2%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	2 (4%)	2 (4%)
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
PERIVASCULAR CUFFING	2 (4%)		1 (2%)
NEPHROPATHY			1 (2%)
NECROSIS, MEDULLARY			1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#URINARY BLADDER	(47)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(46)	(46)
HYPERPLASIA, FOCAL		1 (2%)	
ANGIECTASIS	4 (8%)		
#ADRENAL MEDULLA	(50)	(50)	(47)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#THYROID	(47)	(50)	(49)
CYSTIC FOLLICLES		1 (2%)	2 (4%)
FOLLICULAR CYST, NOS		2 (4%)	
DEGENERATION, CYSTIC	1 (2%)	4 (8%)	
HYPERPLASIA, CYSTIC		1 (2%)	1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)	1 (2%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
*CLITORAL GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	1 (2%)
#UTERUS	(50)	(50)	(50)
HEMATOMA, ORGANIZED		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
PYOMETRA	2 (4%)	3 (6%)	1 (2%)
ABSCESS, NOS		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)		2 (4%)
ADHESION, NOS		1 (2%)	
PERIVASCULAR CUFFING	1 (2%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
#CERVIX UTERI	(50)	(50)	(50)
EDEMA, NOS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	8 (16%)	3 (6%)	4 (8%)
INFLAMMATION CHRONIC SUPPURATIVE		2 (4%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, CYSTIC	26 (52%)	28 (56%)	37 (74%)
DECIDUAL ALTERATION, NOS		1 (2%)	
#OVARY/PAROVARIAN	(50)	(50)	(45)
HEMORRHAGIC CYST			1 (2%)
#OVARY	(50)	(50)	(45)
CYSTIC FOLLICLES			1 (2%)
HEMORRHAGIC CYST	1 (2%)		
ABSCESS, NOS	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
ABSCESS, CHRONIC	26 (52%)	13 (26%)	8 (18%)
ADHESION, NOS	1 (2%)		
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
CORPORA AMYLACEA			1 (2%)
#BRAIN/THALAMUS	(50)	(50)	(50)
PSAMMOMA BODIES		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*BONE	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY		1 (2%)	1 (2%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION CHRONIC SUPPURATIVE	1 (2%)	1 (2%)	
*ABDOMINAL WALL	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	5 (10%)	4 (8%)	2 (4%)
ADHESION, NOS	1 (2%)	1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION CHRONIC SUPPURATIVE		1 (2%)	
NECROSIS, FAT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	14 (28%)	6 (12%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION CHRONIC SUPPURATIVE		2 (4%)	2 (4%)
ADHESION, NOS			1 (2%)
OMENTUM			
INFLAMMATION CHRONIC SUPPURATIVE		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	3	

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

APPENDIX E
ANALYSIS OF PRIMARY TUMORS IN RATS AND MICE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS

	Control	250 mg/kg	500 mg/kg
Skin: Keratoacanthoma			
Overall Rates *(a)*	2/50 (4%)	4/50 (8%)	2/50 (4%)
Adjusted Rates *(b)*	4.7%	8.7%	5.0%
Terminal Rates *(c)*	1/38 (3%)	4/46 (9%)	2/40 (5%)
Life Table Tests *(d)*	P=0.571N	P=0.417	P=0.681N
Incidental Tumor Tests *(d)*	P=0.557	P=0.372	P=0.631
Cochran-Armitage Trend Test *(d)*	P=0.588		
Fisher Exact Tests		P=0.339	P=0.691N
Subcutaneous Tissue: Fibroma			
Overall Rates *(a)*	3/50 (6%)	11/50 (22%)	5/50 (10%)
Adjusted Rates *(b)*	7.4%	23.4%	12.5%
Terminal Rates *(c)*	2/38 (5%)	10/46 (22%)	5/40 (13%)
Life Table Tests *(d)*	P=0.357	P=0.051	P=0.383
Incidental Tumor Tests *(d)*	P=0.337	P=0.014	P=0.369
Cochran-Armitage Trend Test *(d)*	P=0.326		
Fisher Exact Tests		P=0.020	P=0.357
Subcutaneous Tissue: Sarcoma			
Overall Rates *(a)*	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates *(b)*	6.8%	2.2%	0.0%
Terminal Rates *(c)*	1/38 (3%)	1/46 (2%)	0/40 (0%)
Life Table Tests *(d)*	P=0.058N	P=0.269N	P=0.124N
Incidental Tumor Tests *(d)*	P=0.103N	P=0.357N	P=0.223N
Cochran-Armitage Trend Test *(d)*	P=0.060N		
Fisher Exact Tests		P=0.309N	P=0.122N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates *(a)*	0/50 (0%)	3/50 (6%)	0/48 (0%)
Adjusted Rates *(b)*	0.0%	6.5%	0.0%
Terminal Rates *(c)*	0/38 (0%)	3/46 (7%)	0/38 (0%)
Life Table Tests *(d)*	P=0.644	P=0.157	*(e)*
Incidental Tumor Tests *(d)*	P=0.644	P=0.157	*(e)*
Cochran-Armitage Trend Test *(d)*	P=0.629		
Fisher Exact Tests		P=0.121	*(e)*
Hematopoietic System: Monocytic Leukemia			
Overall Rates *(a)*	5/50 (10%)	5/50 (10%)	6/50 (12%)
Adjusted Rates *(b)*	12.2%	10.9%	14.0%
Terminal Rates *(c)*	3/38 (8%)	5/46 (11%)	4/40 (10%)
Life Table Tests *(d)*	P=0.465	P=0.518N	P=0.530
Incidental Tumor Tests *(d)*	P=0.392	P=0.547	P=0.433
Cochran-Armitage Trend Test *(d)*	P=0.436		
Fisher Exact Tests		P=0.630N	P=0.500
Pancreas: Acinar-Cell Adenoma			
Overall Rates *(a)*	22/50 (44%)	27/50 (54%)	37/49 (76%)
Adjusted Rates *(b)*	53.6%	58.7%	82.2%
Terminal Rates *(c)*	19/38 (50%)	27/46 (59%)	32/40 (80%)
Life Table Tests *(d)*	P=0.003	P=0.548	P=0.007
Incidental Tumor Tests *(d)*	P=0.001	P=0.353	P=0.001
Cochran-Armitage Trend Test *(d)*	P=0.001		
Fisher Exact Tests		P=0.212	P=0.001

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Pituitary: Adenoma			
Overall Rates *(a)*	7/50 (14%)	10/50 (20%)	7/49 (14%)
Adjusted Rates *(b)*	17.7%	21.2%	17.5%
Terminal Rates *(c)*	6/38 (16%)	9/46 (20%)	7/40 (18%)
Life Table Tests *(d)*	P=0.515N	P=0.447	P=0.575N
Incidental Tumor Tests *(d)*	P=0.552	P=0.340	P=0.587N
Cochran-Armitage Trend Test *(d)*	P=0.537		
Fisher Exact Tests		P=0.298	P=0.597
Pituitary: Adenoma or Carcinoma			
Overall Rates *(a)*	8/50 (16%)	12/50 (24%)	7/49 (14%)
Adjusted Rates *(b)*	19.8%	25.5%	17.5%
Terminal Rates *(c)*	6/38 (16%)	11/46 (24%)	7/40 (18%)
Life Table Tests *(d)*	P=0.404N	P=0.381	P=0.458N
Incidental Tumor Tests *(d)*	P=0.456N	P=0.217	P=0.483N
Cochran-Armitage Trend Test *(d)*	P=0.467N		
Fisher Exact Tests		P=0.227	P=0.517N
Adrenal: Pheochromocytoma			
Overall Rates *(a)*	8/50 (16%)	5/50 (10%)	8/50 (16%)
Adjusted Rates *(b)*	19.6%	10.9%	20.0%
Terminal Rates *(c)*	6/38 (16%)	5/46 (11%)	8/40 (20%)
Life Table Tests *(d)*	P=0.521N	P=0.180N	P=0.567N
Incidental Tumor Tests *(d)*	P=0.542N	P=0.308N	P=0.589N
Cochran-Armitage Trend Test *(d)*	P=0.557		
Fisher Exact Tests		P=0.277N	P=0.607N
Thyroid: Follicular-Cell Carcinoma			
Overall Rates *(a)*	4/50 (8%)	2/50 (4%)	2/49 (4%)
Adjusted Rates *(b)*	9.9%	4.3%	5.1%
Terminal Rates *(c)*	3/38 (8%)	2/46 (4%)	2/39 (5%)
Life Table Tests *(d)*	P=0.240N	P=0.266N	P=0.330N
Incidental Tumor Tests *(d)*	P=0.283N	P=0.303N	P=0.394N
Cochran-Armitage Trend Test *(d)*	P=0.259N		
Fisher Exact Tests		P=0.339N	P=0.349N
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Overall Rates *(a)*	5/50 (10%)	4/50 (8%)	2/49 (4%)
Adjusted Rates *(b)*	12.5%	8.7%	5.1%
Terminal Rates *(c)*	4/38 (11%)	4/46 (9%)	2/39 (5%)
Life Table Tests *(d)*	P=0.155N	P=0.393N	P=0.211N
Incidental Tumor Tests *(d)*	P=0.184N	P=0.429N	P=0.258N
Cochran-Armitage Trend Test *(d)*	P=0.176N		
Fisher Exact Tests		P=0.500N	P=0.227N
Thyroid: C-Cell Adenoma			
Overall Rates *(a)*	3/50 (6%)	0/50 (0%)	2/49 (4%)
Adjusted Rates *(b)*	7.9%	0.0%	5.1%
Terminal Rates *(c)*	3/38 (8%)	0/46 (0%)	2/39 (5%)
Life Table Tests *(d)*	P=0.378N	P=0.090N	P=0.488N
Incidental Tumor Tests *(d)*	P=0.378N	P=0.090N	P=0.488N
Cochran-Armitage Trend Test *(d)*	P=0.397N		
Fisher Exact Tests		P=0.121N	P=0.510N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Thyroid: C-Cell Carcinoma			
Overall Rates *(a)*	3/50 (6%)	2/50 (4%)	3/49 (6%)
Adjusted Rates *(b)*	7.9%	4.3%	7.3%
Terminal Rates *(c)*	3/38 (8%)	2/46 (4%)	2/39 (5%)
Life Table Tests *(d)*	P=0.576N	P=0.413N	P=0.646N
Incidental Tumor Tests *(d)*	P=0.583	P=0.413N	P=0.658
Cochran-Armitage Trend Test *(d)*	P=0.579		
Fisher Exact Tests		P=0.500N	P=0.651
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates *(a)*	5/50 (10%)	2/50 (4%)	5/49 (10%)
Adjusted Rates *(b)*	13.2%	4.3%	12.3%
Terminal Rates *(c)*	5/38 (13%)	2/46 (4%)	4/39 (10%)
Life Table Tests *(d)*	P=0.558N	P=0.147N	P=0.611N
Incidental Tumor Tests *(d)*	P=0.573N	P=0.147N	P=0.627N
Cochran-Armitage Trend Test *(d)*	P=0.562		
Fisher Exact Tests		P=0.218N	P=0.616
Pancreatic Islets: Islet-Cell Adenoma			
Overall Rates *(a)*	6/50 (12%)	5/50 (10%)	5/49 (10%)
Adjusted Rates *(b)*	15.0%	10.9%	12.0%
Terminal Rates *(c)*	5/38 (13%)	5/46 (11%)	4/40 (10%)
Life Table Tests *(d)*	P=0.409N	P=0.381N	P=0.476N
Incidental Tumor Tests *(d)*	P=0.483N	P=0.411N	P=0.581N
Cochran-Armitage Trend Test *(d)*	P=0.449N		
Fisher Exact Tests		P=0.500N	P=0.514N
Pancreatic Islets: Islet-Cell Carcinoma			
Overall Rates *(a)*	3/50 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates *(b)*	7.9%	0.0%	2.5%
Terminal Rates *(c)*	3/38 (8%)	0/46 (0%)	1/40 (3%)
Life Table Tests *(d)*	P=0.159N	P=0.090N	P=0.287N
Incidental Tumor Tests *(d)*	P=0.159N	P=0.090N	P=0.287N
Cochran-Armitage Trend Test *(d)*	P=0.180N		
Fisher Exact Tests		P=0.122N	P=0.316N
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma			
Overall Rates *(a)*	9/50 (18%)	5/50 (10%)	6/49 (12%)
Adjusted Rates *(b)*	22.7%	10.9%	14.4%
Terminal Rates *(c)*	8/38 (21%)	5/46 (11%)	5/40 (13%)
Life Table Tests *(d)*	P=0.203N	P=0.111N	P=0.262N
Incidental Tumor Tests *(d)*	P=0.253N	P=0.124N	P=0.377N
Cochran-Armitage Trend Test *(d)*	P=0.243N		
Fisher Exact Tests		P=0.194N	P=0.303N
Mammary Gland: Fibroadenoma			
Overall Rates *(a)*	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates *(b)*	10.5%	2.2%	5.0%
Terminal Rates *(c)*	4/38 (11%)	1/46 (2%)	2/40 (5%)
Life Table Tests *(d)*	P=0.215N	P=0.127N	P=0.313N
Incidental Tumor Tests *(d)*	P=0.215N	P=0.127N	P=0.313N
Cochran-Armitage Trend Test *(d)*	P=0.238N		
Fisher Exact Tests		P=0.181N	P=0.339N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Preputial Gland: Cystadenocarcinoma			
Overall Rates *(a)*	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates *(b)*	0.0%	0.0%	7.5%
Terminal Rates *(c)*	0/38 (0%)	0/46 (0%)	3/40 (8%)
Life Table Tests *(d)*	P=0.036	*(e)*	P=0.130
Incidental Tumor Tests *(d)*	P=0.036	*(e)*	P=0.130
Cochran-Armitage Trend Test *(d)*	P=0.037		
Fisher Exact Tests		*(e)*	P=0.121
Preputial Gland: All Adenocarcinoma			
Overall Rates *(a)*	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates *(b)*	0.0%	2.2%	10.0%
Terminal Rates *(c)*	0/38 (0%)	1/46 (2%)	4/40 (10%)
Life Table Tests *(d)*	P=0.025	P=0.538	P=0.070
Incidental Tumor Tests *(d)*	P=0.025	P=0.538	P=0.070
Cochran-Armitage Trend Test *(d)*	P=0.026		
Fisher Exact Tests		P=0.500	P=0.059
Preputial Gland: Adenocarcinoma or Carinoma			
Overall Rates *(a)*	1/50 (2%)	1/50 (2%)	6/50 (12%)
Adjusted Rates *(b)*	2.6%	2.2%	14.3%
Terminal Rates *(c)*	1/38 (3%)	1/46 (2%)	5/40 (13%)
Life Table Tests *(d)*	P=0.023	P=0.719N	P=0.067
Incidental Tumor Tests *(d)*	P=0.040	P=0.719N	P=0.092
Cochran-Armitage Trend Test *(d)*	P=0.023		
Fisher Exact Tests		P=0.753	P=0.056
Preputial Gland: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates *(a)*	2/50 (4%)	1/50 (2%)	6/50 (12%)
Adjusted Rates *(b)*	5.3%	2.2%	14.3%
Terminal Rates *(c)*	2/38 (5%)	1/46 (2%)	5/40 (13%)
Life Table Tests *(d)*	P=0.073	P=0.433N	P=0.150
Incidental Tumor Tests *(d)*	P=0.110	P=0.433N	P=0.194
Cochran-Armitage Trend Test *(d)*	P=0.070		
Fisher Exact Tests		P=0.500N	P=0.134
Testis: Interstitial-Cell Tumor			
Overall Rates *(a)*	48/50 (96%)	48/50 (96%)	37/50 (74%)
Adjusted Rates *(b)*	98.0%	98.0%	80.4%
Terminal Rates *(c)*	37/38 (97%)	45/46 (98%)	31/40 (78%)
Life Table Tests *(d)*	P=0.002N	P=0.033N	P=0.009N
Incidental Tumor Tests *(d)*	P<0.001N	P=0.643N	P=0.003N
Cochran-Armitage Trend Test *(d)*	P<0.001N		
Fisher Exact Tests		P=0.691N	P=0.002N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(e) No statistical tests were done because no tumors were observed in the dosed group or the vehicle control group.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS

	Vehicle Control	250 mg/kg	500 mg/kg
Hematopoietic System: Leukemia			
Overall Rates *(a)*	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates *(b)*	4.8%	6.8%	2.6%
Terminal Rates *(c)*	1/40 (3%)	0/36 (0%)	0/36 (0%)
Life Table Tests *(d)*	P=0.430N	P=0.456	P=0.526N
Incidental Tumor Tests *(d)*	P=0.248N	P=0.658N	P=0.512N
Cochran-Armitage Trend Test *(d)*	P=0.399N		
Fisher Exact Tests		P=0.500	P=0.500N
Pituitary: Adenoma			
Overall Rates *(a)*	18/50 (36%)	10/49 (20%)	14/48 (29%)
Adjusted Rates *(b)*	42.6%	26.9%	41.2%
Terminal Rates *(c)*	16/40 (40%)	8/35 (23%)	14/34 (41%)
Life Table Tests *(d)*	P=0.383N	P=0.124N	P=0.455N
Incidental Tumor Tests *(d)*	P=0.417N	P=0.124N	P=0.540N
Cochran-Armitage Trend Test *(d)*	P=0.256N		
Fisher Exact Tests		P=0.067N	P=0.307N
Pituitary: Carcinoma			
Overall Rates *(a)*	1/50 (2%)	3/49 (6%)	1/48 (2%)
Adjusted Rates *(b)*	2.1%	6.5%	2.1%
Terminal Rates *(c)*	0/40 (0%)	0/35 (0%)	0/34 (0%)
Life Table Tests *(d)*	P=0.590	P=0.284	P=0.746
Incidental Tumor Tests *(d)*	P=0.106N	P=0.557N	P=0.318N
Cochran-Armitage Trend Test *(d)*	P=0.595		
Fisher Exact Tests		P=0.301	P=0.742
Pituitary: Adenoma or Carcinoma			
Overall Rates *(a)*	19/50 (38%)	13/49 (27%)	15/48 (31%)
Adjusted Rates *(b)*	43.8%	31.6%	42.4%
Terminal Rates *(c)*	16/40 (40%)	8/35 (23%)	14/34 (41%)
Life Table Tests *(d)*	P=0.398N	P=0.266N	P=0.462N
Incidental Tumor Tests *(d)*	P=0.265N	P=0.094N	P=0.411N
Cochran-Armitage Trend Test *(d)*	P=0.268N		
Fisher Exact Tests		P=0.158N	P=0.313N
Adrenal: Pheochromocytoma			
Overall Rates *(a)*	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates *(b)*	2.5%	11.1%	0.0%
Terminal Rates *(c)*	1/40 (3%)	4/36 (11%)	0/36 (0%)
Life Table Tests *(d)*	P=0.429N	P=0.149	P=0.521N
Incidental Tumor Tests *(d)*	P=0.429N	P=0.149	P=0.521N
Cochran-Armitage Trend Test *(d)*	P=0.390N		
Fisher Exact Tests		P=0.181	P=0.500N
Thyroid: Follicular-Cell Adenoma or Carcinoma			
Overall Rates *(a)*	0/50 (0%)	3/50 (6%)	1/49 (2%)
Adjusted Rates *(b)*	0.0%	8.3%	2.8%
Terminal Rates *(c)*	0/40 (0%)	3/36 (8%)	1/36 (3%)
Life Table Tests *(d)*	P=0.346	P=0.103	P=0.479
Incidental Tumor Tests *(d)*	P=0.346	P=0.103	P=0.479
Cochran-Armitage Trend Test *(d)*	P=0.372		
Fisher Exact Tests		P=0.121	P=0.495

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Thyroid: C-Cell Adenoma			
Overall Rates *(a)*	6/50 (12%)	4/50 (8%)	4/49 (8%)
Adjusted Rates *(b)*	15.0%	11.1%	10.2%
Terminal Rates *(c)*	6/40 (15%)	4/36 (11%)	2/36 (6%)
Life Table Tests *(d)*	P=0.365N	P=0.436N	P=0.435N
Incidental Tumor Tests *(d)*	P=0.358N	P=0.436N	P=0.424N
Cochran-Armitage Trend Test *(d)*	P=0.314N		
Fisher Exact Tests		P=0.371N	P=0.384N
Thyroid: C-Cell Carcinoma			
Overall Rates *(a)*	4/50 (8%)	5/50 (10%)	4/49 (8%)
Adjusted Rates *(b)*	10.0%	13.9%	11.1%
Terminal Rates *(c)*	4/40 (10%)	5/36 (14%)	4/36 (11%)
Life Table Tests *(d)*	P=0.505	P=0.434	P=0.585
Incidental Tumor Tests *(d)*	P=0.505	P=0.434	P=0.585
Cochran-Armitage Trend Test *(d)*	P=0.558		
Fisher Exact Tests		P=0.500	P=0.631
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates *(a)*	9/50 (18%)	9/50 (18%)	8/49 (16%)
Adjusted Rates *(b)*	22.5%	25.0%	20.8%
Terminal Rates *(c)*	9/40 (23%)	9/36 (25%)	6/36 (17%)
Life Table Tests *(d)*	P=0.544N	P=0.506	P=0.592N
Incidental Tumor Tests *(d)*	P=0.538N	P=0.506	P=0.584N
Cochran-Armitage Trend Test *(d)*	P=0.466N		
Fisher Exact Tests		P=0.603N	P=0.519N
Mammary Gland: Fibroadenoma			
Overall Rates *(a)*	16/50 (32%)	17/50 (34%)	16/50 (32%)
Adjusted Rates *(b)*	36.1%	43.4%	39.3%
Terminal Rates *(c)*	12/40 (30%)	14/36 (39%)	12/36 (33%)
Life Table Tests *(d)*	P=0.411	P=0.360	P=0.457
Incidental Tumor Tests *(d)*	P=0.525	P=0.404	P=0.510N
Cochran-Armitage Trend Test *(d)*	P=0.542		
Fisher Exact Tests		P=0.500	P=0.585N
Preputial/Clitoral Gland: Adenoma			
Overall Rates *(a)*	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates *(b)*	2.5%	0.0%	8.3%
Terminal Rates *(c)*	1/40 (3%)	0/36 (0%)	3/36 (8%)
Life Table Tests *(d)*	P=0.156	P=0.521N	P=0.268
Incidental Tumor Tests *(d)*	P=0.156	P=0.521N	P=0.268
Cochran-Armitage Trend Test *(d)*	P=0.176		
Fisher Exact Tests		P=0.500N	P=0.309
Preputial/Clitoral Gland: Adenoma or Carcinoma			
Overall Rates *(a)*	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates *(b)*	5.0%	0.0%	13.9%
Terminal Rates *(c)*	2/40 (5%)	0/36 (0%)	5/36 (14%)
Life Table Tests *(d)*	P=0.097	P=0.262N	P=0.175
Incidental Tumor Tests *(d)*	P=0.097	P=0.262N	P=0.175
Cochran-Armitage Trend Test *(d)*	P=0.118		
Fisher Exact Tests		P=0.247N	P=0.218

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates *(a)*	12/50 (24%)	9/50 (18%)	18/50 (36%)
Adjusted Rates *(b)*	27.7%	23.3%	44.4%
Terminal Rates *(c)*	9/40 (23%)	7/36 (19%)	14/36 (39%)
Life Table Tests *(d)*	P=0.070	P=0.417N	P=0.090
Incidental Tumor Tests *(d)*	P=0.107	P=0.349N	P=0.145
Cochran-Armitage Trend Test *(d)*	P=0.105		
Fisher Exact Tests		P=0.312N	P=0.138
Uterus: Endometrial Stromal Sarcoma			
Overall Rates *(a)*	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted Rates *(b)*	2.5%	7.0%	6.9%
Terminal Rates *(c)*	1/40 (3%)	1/36 (3%)	0/36 (0%)
Life Table Tests *(d)*	P=0.225	P=0.282	P=0.287
Incidental Tumor Tests *(d)*	P=0.413	P=0.577	P=0.426
Cochran-Armitage Trend Test *(d)*	P=0.238		
Fisher Exact Tests		P=0.309	P=0.309
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates *(a)*	13/50 (26%)	12/50 (24%)	19/50 (38%)
Adjusted Rates *(b)*	30.0%	29.1%	45.7%
Terminal Rates *(c)*	10/40 (25%)	8/36 (22%)	14/36 (39%)
Life Table Tests *(d)*	P=0.078	P=0.564	P=0.093
Incidental Tumor Tests *(d)*	P=0.147	P=0.417N	P=0.146
Cochran-Armitage Trend Test *(d)*	P=0.114		
Fisher Exact Tests		P=0.500N	P=0.142
Uterus: Adenocarcinoma			
Overall Rates *(a)*	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates *(b)*	4.6%	7.8%	0.0%
Terminal Rates *(c)*	1/40 (3%)	2/36 (6%)	0/36 (0%)
Life Table Tests *(d)*	P=0.234N	P=0.449	P=0.264N
Incidental Tumor Tests *(d)*	P=0.222N	P=0.443	P=0.251N
Cochran-Armitage Trend Test *(d)*	P=0.202N		
Fisher Exact Tests		P=0.500	P=0.247N
Uterus: Adenocarcinoma or Carcinoma			
Overall Rates *(a)*	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates *(b)*	7.1%	7.8%	2.8%
Terminal Rates *(c)*	2/40 (5%)	2/36 (6%)	1/36 (3%)
Life Table Tests *(d)*	P=0.279N	P=0.608	P=0.346N
Incidental Tumor Tests *(d)*	P=0.269N	P=0.605	P=0.335N
Cochran-Armitage Trend Test *(d)*	P=0.238N		
Fisher Exact Tests		P=0.661	P=0.309N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Uterus: Adenoma, Adenocarcinoma, or Carcinoma			
Overall Rates *(a)*	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates *(b)*	9.5%	7.8%	2.8%
Terminal Rates *(c)*	3/40 (7%)	2/36 (6%)	1/36 (3%)
Life Table Tests *(d)*	P=0.166N	P=0.560N	P=0.215N
Incidental Tumor Tests *(d)*	P=0.158N	P=0.565N	P=0.208N
Cochran-Armitage Trend Test *(d)*	P=0.133N		
Fisher Exact Tests		P=0.500N	P=0.181N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates *(a)*	7/50 (14%)	4/49 (8%)	6/50 (12%)
Adjusted Rates *(b)*	18.4%	10.7%	14.8%
Terminal Rates *(c)*	7/38 (18%)	2/33 (6%)	5/39 (13%)
Life Table Tests *(d)*	P=0.413N	P=0.033N	P=0.476N
Incidental Tumor Tests *(d)*	P=0.342N	P=0.263N	P=0.409N
Cochran-Armitage Trend Test *(d)*	P=0.438N		
Fisher Exact Tests		P=0.274N	P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates *(a)*	5/50 (10%)	3/49 (6%)	2/50 (4%)
Adjusted Rates *(b)*	13.2%	9.1%	5.1%
Terminal Rates *(c)*	5/38 (13%)	3/33 (9%)	2/39 (5%)
Life Table Tests *(d)*	P=0.153N	P=0.435N	P=0.205N
Incidental Tumor Tests *(d)*	P=0.153N	P=0.435N	P=0.205N
Cochran-Armitage Trend Test *(d)*	P=0.159N		
Fisher Exact Tests		P=0.369N	P=0.218N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates *(a)*	12/50 (24%)	7/49 (14%)	7/50 (14%)
Adjusted Rates *(b)*	31.6%	19.3%	17.4%
Terminal Rates *(c)*	12/38 (32%)	5/33 (15%)	6/39 (15%)
Life Table Tests *(d)*	P=0.107N	P=0.235N	P=0.134N
Incidental Tumor Tests *(d)*	P=0.078N	P=0.187N	P=0.103N
Cochran-Armitage Trend Test *(d)*	P=0.118N		
Fisher Exact Tests		P=0.166N	P=0.154N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates *(a)*	3/50 (6%)	2/49 (4%)	1/50 (2%)
Adjusted Rates *(b)*	7.6%	5.5%	2.6%
Terminal Rates *(c)*	2/38 (5%)	1/33 (3%)	1/39 (3%)
Life Table Tests *(d)*	P=0.213N	P=0.531N	P=0.290N
Incidental Tumor Tests *(d)*	P=0.210N	P=0.415N	P=0.300N
Cochran-Armitage Trend Test *(d)*	P=0.223N		
Fisher Exact Tests		P=0.510N	P=0.309N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates *(a)*	5/50 (10%)	7/49 (14%)	3/50 (6%)
Adjusted Rates *(b)*	12.7%	17.7%	7.3%
Terminal Rates *(c)*	4/38 (11%)	3/33 (9%)	2/39 (5%)
Life Table Tests *(d)*	P=0.286N	P=0.334	P=0.334N
Incidental Tumor Tests *(d)*	P=0.220N	P=0.513	P=0.267N
Cochran-Armitage Trend Test *(d)*	P=0.309N		
Fisher Exact Tests		P=0.365	P=0.358N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates *(a)*	5/50 (10%)	9/49 (18%)	3/50 (6%)
Adjusted Rates *(b)*	12.7%	21.9%	7.3%
Terminal Rates *(c)*	4/38 (11%)	3/33 (9%)	2/39 (5%)
Life Table Tests *(d)*	P=0.291N	P=0.172	P=0.334N
Incidental Tumor Tests *(d)*	P=0.194N	P=0.384	P=0.267N
Cochran-Armitage Trend Test *(d)*	P=0.319N		
Fisher Exact Tests		P=0.183	P=0.358N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Circulatory System: Hemangiosarcoma			
Overall Rates *(a)*	4/50 (8%)	3/49 (6%)	1/50 (2%)
Adjusted Rates *(b)*	10.1%	8.8%	2.6%
Terminal Rates *(c)*	3/38 (8%)	2/33 (6%)	1/39 (3%)
Life Table Tests *(d)*	P=0.130N	P=0.559N	P=0.169N
Incidental Tumor Tests *(d)*	P=0.097N	P=0.408N	P=0.176N
Cochran-Armitage Trend Test *(d)*	P=0.134N		
Fisher Exact Tests		P=0.512N	P=0.181N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates *(a)*	4/50 (8%)	4/49 (8%)	1/50 (2%)
Adjusted Rates *(b)*	10.1%	11.8%	2.6%
Terminal Rates *(c)*	3/38 (8%)	3/33 (9%)	1/39 (3%)
Life Table Tests *(d)*	P=0.142N	P=0.579	P=0.169N
Incidental Tumor Tests *(d)*	P=0.110N	P=0.573N	P=0.176N
Cochran-Armitage Trend Test *(d)*	P=0.147N		
Fisher Exact Tests		P=0.631	P=0.181N
Liver: Adenoma			
Overall Rates *(a)*	0/50 (0%)	5/49 (10%)	13/50 (26%)
Adjusted Rates *(b)*	0.0%	13.0%	33.3%
Terminal Rates *(c)*	0/38 (0%)	3/33 (9%)	13/39 (33%)
Life Table Tests *(d)*	P<0.001	P=0.030	P<0.001
Incidental Tumor Tests *(d)*	P<0.001	P=0.023	P<0.001
Cochran-Armitage Trend Test *(d)*	P<0.001		
Fisher Exact Tests		P=0.027	P<0.001
Liver: Carcinoma			
Overall Rates *(a)*	10/50 (20%)	14/49 (29%)	12/50 (24%)
Adjusted Rates *(b)*	24.3%	35.9%	25.8%
Terminal Rates *(c)*	7/38 (18%)	9/33 (27%)	5/39 (13%)
Life Table Tests *(d)*	P=0.427	P=0.183	P=0.463
Incidental Tumor Tests *(d)*	P=0.536	P=0.379	P=0.548N
Cochran-Armitage Trend Test *(d)*	P=0.363		
Fisher Exact Tests		P=0.224	P=0.405
Liver: Adenoma or Carcinoma			
Overall Rates *(a)*	10/50 (20%)	18/49 (37%)	23/50 (46%)
Adjusted Rates *(b)*	24.3%	45.1%	49.8%
Terminal Rates *(c)*	7/38 (18%)	12/33 (36%)	16/39 (41%)
Life Table Tests *(d)*	P=0.013	P=0.042	P=0.014
Incidental Tumor Tests *(d)*	P=0.009	P=0.098	P=0.019
Cochran-Armitage Trend Test *(d)*	P=0.004		
Fisher Exact Tests		P=0.052	P=0.005
Forestomach: Squamous Cell Papilloma			
Overall Rates *(a)*	3/49 (6%)	3/48 (6%)	9/49 (18%)
Adjusted Rates *(b)*	7.9%	9.1%	23.1%
Terminal Rates *(c)*	3/38 (8%)	3/33 (9%)	9/39 (23%)
Life Table Tests *(d)*	P=0.038	P=0.597	P=0.065
Incidental Tumor Tests *(d)*	P=0.038	P=0.597	P=0.065
Cochran-Armitage Trend Test *(d)*	P=0.034		
Fisher Exact Tests		P=0.651	P=0.060

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates *(a)*	4/49 (8%)	4/48 (8%)	11/49 (22%)
Adjusted Rates *(b)*	10.0%	11.3%	28.2%
Terminal Rates *(c)*	3/38 (8%)	3/33 (9%)	11/39 (28%)
Life Table Tests *(d)*	P=0.032	P=0.588	P=0.052
Incidental Tumor Tests *(d)*	P=0.028	P=0.619	P=0.051
Cochran-Armitage Trend Test *(d)*	P=0.025		
Fisher Exact Tests		P=0.631	P=0.045
Thyroid: Follicular-Cell Adenoma			
Overall Rates *(a)*	1/49 (2%)	3/49 (6%)	4/47 (9%)
Adjusted Rates *(b)*	2.6%	9.1%	10.8%
Terminal Rates *(c)*	1/38 (3%)	3/33 (9%)	4/37 (11%)
Life Table Tests *(d)*	P=0.129	P=0.256	P=0.171
Incidental Tumor Tests *(d)*	P=0.129	P=0.256	P=0.171
Cochran-Armitage Trend Test *(d)*	P=0.122		
Fisher Exact Tests		P=0.309	P=0.168
Harderian Gland: Adenoma			
Overall Rates *(a)*	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted Rates *(b)*	5.3%	0.0%	7.7%
Terminal Rates *(c)*	2/38 (5%)	0/33 (0%)	3/39 (8%)
Life Table Tests *(d)*	P=0.402	P=0.270N	P=0.512
Incidental Tumor Tests *(d)*	P=0.402	P=0.270N	P=0.512
Cochran-Armitage Trend Test *(d)*	P=0.391		
Fisher Exact Tests		P=0.252N	P=0.500

(a) Number of tumor bearing animals number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates *(a)*	1/49 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates *(b)*	4.2%	8.9%	3.3%
Terminal Rates *(c)*	0/14 (0%)	0/18 (0%)	1/30 (3%)
Life Table Tests *(d)*	P=0.474N	P=0.354	P=0.634N
Incidental Tumor Tests *(d)*	P=0.486	P=0.206	P=0.771
Cochran-Armitage Trend Test *(d)*	P=0.603N		
Fisher Exact Tests		P=0.316	P=0.748N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates *(a)*	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates *(b)*	24.2%	9.7%	10.0%
Terminal Rates *(c)*	3/15 (20%)	1/18 (6%)	3/30 (10%)
Life Table Tests *(d)*	P=0.139N	P=0.235N	P=0.173N
Incidental Tumor Tests *(d)*	P=0.194N	P=0.200N	P=0.231N
Cochran-Armitage Trend Test *(d)*	P=0.417N		
Fisher Exact Tests		P=0.339N	P=0.500N
Hematopoietic System: All Malignant Lymphoma			
Overall Rates *(a)*	5/50 (10%)	6/50 (12%)	7/50 (14%)
Adjusted Rates *(b)*	30.5%	27.8%	21.0%
Terminal Rates *(c)*	4/15 (27%)	4/18 (22%)	5/30 (17%)
Life Table Tests *(d)*	P=0.354N	P=0.625N	P=0.430N
Incidental Tumor Tests *(d)*	P=0.521N	P=0.621	P=0.586N
Cochran-Armitage Trend Test *(d)*	P=0.322		
Fisher Exact Tests		P=0.500	P=0.380
Hematopoietic System: Leukemia			
Overall Rates *(a)*	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates *(b)*	2.7%	11.9%	2.4%
Terminal Rates *(c)*	0/15 (0%)	1/18 (6%)	0/30 (0%)
Life Table Tests *(d)*	P=0.492N	P=0.349	P=0.740N
Incidental Tumor Tests *(d)*	P=0.572	P=0.356	P=0.693
Cochran-Armitage Trend Test *(d)*	P=0.610		
Fisher Exact Tests		P=0.309	P=0.753N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates *(a)*	6/50 (12%)	9/50 (18%)	8/50 (16%)
Adjusted Rates *(b)*	32.4%	37.6%	22.9%
Terminal Rates *(c)*	4/15 (27%)	5/18 (28%)	5/30 (17%)
Life Table Tests *(d)*	P=0.317N	P=0.417	P=0.426N
Incidental Tumor Tests *(d)*	P=0.541N	P=0.407	P=0.617N
Cochran-Armitage Trend Test *(d)*	P=0.339		
Fisher Exact Tests		P=0.288	P=0.387
Liver: Adenoma			
Overall Rates *(a)*	0/50 (0%)	0/50 (0%)	6/50 (12%)
Adjusted Rates *(b)*	0.0%	0.0%	17.4%
Terminal Rates *(c)*	0/15 (0%)	0/18 (0%)	3/30 (10%)
Life Table Tests *(d)*	P=0.012	*(e)*	P=0.067
Incidental Tumor Tests *(d)*	P=0.002	*(e)*	P=0.013
Cochran-Armitage Trend Test *(d)*	P=0.003		
Fisher Exact Tests		*(e)*	P=0.013

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Liver: Carcinoma			
Overall Rates *(a)*	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates *(b)*	6.7%	0.0%	12.6%
Terminal Rates *(c)*	1/15 (7%)	0/18 (0%)	3/30 (10%)
Life Table Tests *(d)*	P=0.209	P=0.464N	P=0.401
Incidental Tumor Tests *(d)*	P=0.150	P=0.464N	P=0.302
Cochran-Armitage Trend Test *(d)*	P=0.082		
Fisher Exact Tests		P=0.500N	P=0.181
Liver: Adenoma or Carcinoma			
Overall Rates *(a)*	1/50 (2%)	0/50 (0%)	10/50 (20%)
Adjusted Rates *(b)*	6.7%	0.0%	28.7%
Terminal Rates *(c)*	1/15 (7%)	0/18 (0%)	6/30 (20%)
Life Table Tests *(d)*	P=0.007	P=0.464N	P=0.050
Incidental Tumor Tests *(d)*	P=0.001	P=0.464N	P=0.008
Cochran-Armitage Trend Test *(d)*	P<0.001		
Fisher Exact Tests		P=0.500N	P=0.004
Forestomach: Squamous Cell Papilloma			
Overall Rates *(a)*	0/50 (0%)	0/50 (0%)	4/48 (8%)
Adjusted Rates *(b)*	0.0%	0.0%	13.3%
Terminal Rates *(c)*	0/15 (0%)	0/18 (0%)	4/30 (13%)
Life Table Tests *(d)*	P=0.054	*(e)*	P=0.180
Incidental Tumor Tests *(d)*	P=0.054	*(e)*	P=0.180
Cochran-Armitage Trend Test *(d)*	P=0.013		
Fisher Exact Tests		*(e)*	P=0.054
Pituitary: Adenoma			
Overall Rates *(a)*	3/48 (6%)	4/46 (9%)	3/46 (7%)
Adjusted Rates *(b)*	20.0%	22.3%	10.7%
Terminal Rates *(c)*	3/15 (20%)	3/16 (19%)	3/28 (11%)
Life Table Tests *(d)*	P=0.244N	P=0.561	P=0.355N
Incidental Tumor Tests *(d)*	P=0.276N	P=0.594	P=0.355N
Cochran-Armitage Trend Test *(d)*	P=0.557		
Fisher Exact Tests		P=0.476	P=0.641
Pituitary: Adenoma or Carcinoma			
Overall Rates *(a)*	3/48 (6%)	5/46 (11%)	3/46 (7%)
Adjusted Rates *(b)*	20.0%	28.3%	10.7%
Terminal Rates *(c)*	3/15 (20%)	4/16 (25%)	3/28 (11%)
Life Table Tests *(d)*	P=0.225N	P=0.408	P=0.355N
Incidental Tumor Tests *(d)*	P=0.255N	P=0.439	P=0.355N
Cochran-Armitage Trend Test *(d)*	P=0.552		
Fisher Exact Tests		P=0.333	P=0.641

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Thyroid: Follicular-Cell Adenoma			
Overall Rates *(a)*	3/47 (6%)	2/50 (4%)	2/49 (4%)
Adjusted Rates *(b)*	23.1%	11.1%	5.9%
Terminal Rates *(c)*	3/13 (23%)	2/18 (11%)	1/30 (3%)
Life Table Tests *(d)*	P=0.135N	P=0.347N	P=0.204N
Incidental Tumor Tests *(d)*	P=0.178N	P=0.347N	P=0.275N
Cochran-Armitage Trend Test *(d)*	P=0.388N		
Fisher Exact Tests		P=0.471N	P=0.480N

(a) Number of tumor bearing animals/number of animals examined at the site.
(b) Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
(c) Observed tumor incidence at terminal kill.
(d) Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidences are the P-values corresponding to pairwise comparisons between that dosed group and the 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 non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence is indicated by (N).
(e) No statistical tests were done because no tumors were observed in the dosed group or the vehicle control group.

APPENDIX F
HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE

TABLE F1. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	0/50	1/50	1/50
Benzyl Acetate	1/50	1/50	2/50
Allyl Isovalerate	0/50	0/50	0/50
HC Red 3	1/50	0/50	1/50
Allyl Isothiocyanate	0/50	4/50 *(b)*	4/50 *(b)*
Geranyl acetate	3/50	0/50	3/50
Total	5/300 (1.7%)	6/300 (2.0%)	11/300 (3.7%)
SD *(c)*	2.34%	3.10%	2.94%
Range			
High	3/50	4/50	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	20/1,100 (1.8%)	22/1,100 (2.0%) *(d)*	42/1,100 (3.8%) (d)
SD *(c)*	3.43%	2.23%	3.70%
Range			
High	7/50	4/50	7/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Adenocarcinoma.
(c) Standard deviation.
(d) Includes five adenocarcinomas; no cystadenomas or cystadenocarcinomas have been observed in vehicle control groups.

TABLE F2. HISTORICAL INCIDENCE OF PREPUTIAL/CLITORAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	0/50	2/50	2/50
Benzyl Acetate	1/50	1/50	2/50
Allyl Isovalerate	0/50	0/50	0/50
HC Red 3	0/50	1/50	1/50
Allyl Isothiocyanate	0/50	0/50	
Geranyl acetate	1/50	0/50	1/50
Total	2/300 (0.7%)	4/300 (1.3%)	6/300 (2.0%)
SD *(b)*	1.03%	1.63%	1.79%
Range			
High	1/50	2/50	2/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	11/1,100 (1.0%)	16/1,100 (1.5%) *(c)*	27/1,100 (2.5%) (c)
SD *(b)*	1.35%	1.53%	1.63%
Range			
High	2/50	2/50	3/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Standard deviation.
(c) Includes one adenocarcinoma.

TABLE F3. HISTORICAL INCIDENCE OF PANCREATIC ACINAR-CELL TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE *(a)*

	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute	
Ethyl Acrylate	0/49
Benzyl Acetate	1/50
Allyl Isovalerate	1/50
HC Red 3	11/50 *(b)*
Allyl Isothiocyanate	1/50 *(c)*
Geranyl Acetate	0/49
Total	14/298 (4.7%)
SD *(d)*	8.55%
Range	
High	11/50
Low	0/49
Overall Historical Incidence	
Total	47/1,086 (4.3%) *(e)*
SD *(d)*	7.37%
Range	
High	14/50
Low	0/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) An acinar-cell carcinoma was also present in one animal with an acinar-cell adenoma.
(c) Adenoma, NOS.
(d) Standard deviation.
(e) Two acinar-cell carcinomas were observed, one of which was in an animal also bearing an acinar-cell adenoma.

TABLE F4. HISTORICAL INCIDENCE OF STOMACH AND FORESTOMACH SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	0/48	0/48	0/48
Benzyl acetate	1/49	1/49	2/49
Allyl Isovalerate	0/50	0/50	0/50
HC Red 3	0/50	0/50	0/50
Allyl Isothiocyanate	0/49	0/49	0/49
Geranyl Aetate	0/50	0/50	0/50
Total	1/296 (0.3%)	1/296 (0.3%)	2/296 (0.7%)
SD *(b)*	0.83%	0.83%	1.67%
Range			
High	1/49	1/49	2/49
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	9/1,070 (0.8%) *(c)*	5/1,070 (0.5%)	14/1,070 (1.3%) *(c)*
SD (b)	1.54%	0.88%	1.65%
Range			
High	2/46	1/47	2/46
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Standard deviation.
(c) Includes one papilloma, NOS.

TABLE F5. HISTORICAL INCIDENCE OF STOMACH AND FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	1/50	0/50	1/50
Benzyl Acetate	0/50	0/50	0/50
Allyl Isovalerate	1/50	0/50	1/50
HC Red 3	0/50	0/50	0/50
Allyl Isothiocyanate	0/47	0/47	0/47
Geranyl Acetate	0/50	0/50	0/50
Total	2/297 (0.7%)	0/297 (0.0%)	2/297 (0.7%)
SD *(b)*	1.03%	--	1.03%
Range			
High	1/50	0/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
Total	3/1,073 (0.3%)	0/1,073 (0.0%)	3/1,073 (0.3%)
SD *(b)*	0.74%	--	0.74%
Range			
High	1/43	0/50	1/43
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Standard deviation.

TABLE F6. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	6/49	12/49	17/49
Benzyl Acetate	0/50	10/50	10/50
Allyl Isovalerate	7/50	18/50	23/50
HC Red 3	11/50	17/50	25/50
Allyl Isothiocyanate	9/49	13/49	21/49
Geranyl Acetate	3/50	11/50	13/50
Total	36/298 (12.1%)	81/298 (27.2%)	109/298 (36.6%)
SD *(b)*	8.06%	6.49%	11.82%
Range			
High	11/50	18/50	25/50
Low	0/50	10/50	10/50
Overall Historical Incidence			
Total	140/1,091 (12.8%)	238/1,091 (21.8%)	357/1,091 (32.7%)
SD *(b)*	6.82%	7.75%	9.63%
Range			
High	14/50	19/50	25/50
Low	0/50	5/50	7/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Standard deviation.

TABLE F7. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE *(a)*

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Ethyl Acrylate	1/50	2/50	3/50
Benzyl Acetate	0/50	1/50	1/50
Allyl Isovalerate	2/50	1/50	3/50
HC Red 3	4/50	0/50	4/50
Allyl Isothiocyanate	2/50	0/50	2/50
Geranyl acetate	2/50	3/50	5/50
Total	11/300 (3.7%)	7/300 (2.3%)	18/300 (6.0%)
SD *(b)*	2.66%	2.34%	2.83%
Range			
High	4/50	3/50	5/50
Low	0/50	0/50	1/50
Overall Historical Incidence			
Total	41/1,092 (3.8%)	34/1,092 (3.1%)	74/1,092 (6.8%)
SD *(b)*	2.65%	2.29%	3.63%
Range			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of August 3, 1984 for studies of at least 104 weeks.
(b) Standard deviation.

APPENDIX G
GENETIC TOXICOLOGY OF BENZYL ACETATE

TABLE G1. MUTAGENICITY OF BENZYL ACETATE IN SALMONELLA

Strain	Dose (μg/plate)	Revertants/plate *(a)*		
		-S9	+S9 (rat)	+S9 (hamster)
TA100	0	97 ± 3.5	105 ± 14.9	102 ± 7.3
	33	102 ± 6.7	122 ± 2.9	67 ± 2.7
	100	101 ± 4.0	110 ± 12.3	97 ± 9.6
	333	85 ± 5.8	99 ± 12.1	93 ± 2.7
	1000	91 ± 14.4	78 ± 4.1	104 ± 15.5
	3333	58 ± 11.7	95 ± 6.5	84 ± 9.0
TA1535	0	8 ± 0.3	6 ± 1.3	7 ± 1.5
	33	5 ± 0.9	6 ± 1.5	6 ± 1.2
	100	4 ± 0.6	6 ± 1.2	8 ± 1.2
	333	5 ± 0.6	5 ± 0.3	2 ± 0.9
	1000	4 ± 0.6	8 ± 3.0	3 ± 1.2
	3333	3 ± 0.3	5 ± 2.3	1 ± 0.7
TA1537	0	2 ± 0.0	7 ± 1.3	6 ± 1.2
	100	2 ± 1.0	6 ± 1.2	8 ± 2.3
	333	5 ± 1.0	9 ± 0.3	4 ± 0.9
	1000	1 ± 0.7	7 ± 3.2	4 ± 1.2
	3333	Toxic	5 ± 1.5	3 ± 0.3
	10000	Toxic	4 ± 1.3	6 ± 1.2
TA98	0	12 ± 2.8	20 ± 1.2	16 ± 2.6
	100	11 ± 1.2	23 ± 2.5	20 ± 1.8
	333	13 ± 0.3	24 ± 1.9	20 ± 3.8
	1000	15 ± 3.5	20 ± 3.2	16 ± 1.9
	3333	12 ± 2.3	19 ± 4.8	19 ± 2.3
	10000	8 ± 1.0	18 ± 4.1	12 ± 1.3

(a) The S9 fractions were prepared from the livers of Aroclor-1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (DMSO) were incubated for 20 min at 37°C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37°C for 48 hr (Haworth et al. 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE G2. CYTOGENETIC EFFECTS OF BENZYL ACETATE IN CHINESE HAMSTER OVARY (CHO) CELLS

Sister-Chromatid Exchanges *(a)*				Chromosome Aberrations *(b)*			
-S9		+S9 *(c)*		-S9		+S9 *(c)*	
Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	Abs/100 Cells (% cells w/abs)	Dose (μg/ml)	Abs/100 Cells (% cells w/abs)
DMSO (10 μl)	10.36	DMSO (10 μl)	9.22	DMSO (10 μl)	4 (3)	DMSO (10 μl)	4 (4)
50	8.98	500	9.68	500	5 (5)	3000	10 (9)
160	9.46	1600	9.86	1000	5 (5)	4000	9 (8)
500	9.74	5000	10.30	1500	11 (9)	5000	9 (9)
Mitomycin C (0.005)	23.48	Cyclophosphamide (1)	17.24	Mitomycin C (0.15)	17 (30)	Cyclophosphamide (15)	18 (14)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hr at 37°C. The BrdU was added and incubation continued for 24 hr. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hr. Cells were then collected by mitotic shake-off, treated for 3 min with KCl (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Straining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978). In the presence of S9, cells were incubated with test compound or solvent for 2 hr at 37°C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hr, with colcemid (0.1 μg/ml) present for the final 2-3 hr.

(b) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hr at 37°C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hr of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. In the presence of S9, cells were incubated with test compound or solvent for 2 hr at 37°C. Cells were then washed, medium was added, and incubation continued for 8-10 hr. Colcemid (0.1 μg/ml) was added for the last 2-3 hr of incubation, then cells were harvested and fixed as above.

(c) S9 from the livers of Aroclor-1254-induced male Sprague-Dawley rats.

TABLE G3. MUTAGENICITY OF BENZYL ACETATE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE PRESENCE OF S9

Compound *(a)* (Dose)	Total Mutant Clones	Cloning Efficiency (%)	Relative Total Growth (%)	Mutation Frequency (Mutants/10^6 clonable cells)
DMSO	285	98.6	101.3	136
(1%)	222	112.0	112.4	93
	216	89.2	86.4	114
3-Methylchol-	392	32.7	8.1	564
anthrene	63	6.1	0.6	485
(6 μg/ml)				
Benzyl Acetate (μl/ml)				
0.25	242	116.7	119.9	98
	229	94.6	99.9	114
0.50	287	96.0	72.4	141
	460	93.4	84.7	232
0.75	517	87.1	63.6	279
	408	83.1	67.1	231
1.00	511	99.1	68.4	243
	480	85.4	57.6	264
1.25	618	56.0	30.8	519
	663	83.5	53.7	374

(a) Experiments were performed twice, and all doses were tested in duplicate, except the solvent control (DMSO), which was tested in triplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells ($6x10^5$/ml) were treated for 4 hr at 37° C in medium, washed, resuspended in medium, and incubated for 48 hr at 37° C. After expression, $3x10^6$ cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells. S9 was prepared from the livers of Aroclor-1254-induced male Fischer 344 rats.

TABLE G4. MUTAGENICITY OF BENZYL ACETATE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9

Compound *(a)* (Dose)	Total Mutant Clones	Cloning Efficiency (%)	Relative Total Growth (%)	Mutation Frequency (Mutants/10^6 clonable cells)
DMSO	130	99.7	108.7	72
(1%)	130	100.0	91.0	72
Hycanthone	387	53.1	48.7	405
(10 μg/ml)	555	61.9	110.4	498
Benzyl Acetate (μl/ml)				
0.25	173	103.9	117.5	93
	130	113.1	127.9	64
0.50	96	103.9	101.3	51
	130	105.0	104.5	69
0.75	128	95.0	77.6	75
	170	102.8	103.9	92
1.00	186	100.8	59.5	102
	139	94.4	50.5	82

(a) Experiments were performed twice, and all doses were tested in duplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells ($6x10^5$/ml) were treated for 4 hr at 37° C in medium, washed, resuspended in medium, and incubated for 48 hr at 37° C. After expression, $3x10^6$ cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

APPENDIX H
BENZYL ACETATE METABOLISM AND DISPOSITION IN RATS AND MICE

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METHODS

Chemicals: Benzyl acetate (ring-UL-^{14}C) was purchased from Midwest Research Institute (Kansas City, Missouri); unlabeled benzyl acetate was purchased from Aldrich Chemical Co. (Milwaukee, WI). Both labeled and unlabeled BA were determined to be greater than 99% chemically and radiochemically pure by HPLC analysis. BA was administered by gavage in corn oil (Mazola); a preparation of Emulphor EL-620 (GAF, New York, N.Y.): ethanol:water (1:1:4) was used for iv dosing.

Animals: Adult (8-10 wk old, 180-220g) male Fischer 344 rats and adult (6-8 wk old, 19-26g) male B6C3F1 mice were purchased from Charles River Breeders (Kingston, N.Y.). Each animal received pelleted NIH 31 rat chow and water ad libitum throughout the study. Animals dosed with ^{14}C-labeled BA preparations were transferred to individual metabolism cages to provide separate collection of urine, feces, exhaled $^{14}CO_2$, and volatilized BA or metabolites.

Dosing: For mice, the dosing preparation for intravenous dosing was a solution of Emulphor:ethanol:water (1:1:4) containing 29 μCi benzyl acetate-ring ^{14}C and sufficient unlabeled BA to total 10 mg BA per ml. This preparation was injected into a tail vein at 1 μl/g body wt to deliver a dose of 10 mg/kg. For rats, the dosing preparation for intravenous administration was a solution of Emulphor:ethanol:water (1:1:8) containing 10 μCi benzyl acetate-ring ^{14}C and sufficient unlabeled BA to total 5 mg BA per ml and was injected into a tail vein to deliver a dose of 5 mg/kg. Oral doses for rats and mice were administered in corn oil. For mice, the oral doses contained approximately 12 μCi benzyl acetate-ring ^{14}C per ml and sufficient unlabeled BA to administer doses at 10, 100 or 1,000 mg/kg in 10 ml corn oil/kg body weight. Mice were treated with an 18 gauge x 1 1/2 in. feeding needle (Popper and Sons, Hyde Park, N.Y.). The oral dose for rats contained approximately 2 μCi benzyl acetate-ring ^{14}C per ml and sufficient unlabeled BA to administer doses of 5, 50 or 500 mg/kg in 5 ml corn oil/kg body weight. Rats were treated with an 18 gauge x 2 1/2 in. feeding needle. For repeated-dose studies rats and mice received unlabeled BA by gavage in corn oil as described above at 500 or 1,000 mg/kg, respectively. Doses were administered 5 days per week for 14 days. Treatment was staggered to allow sacrifice of mice on Thursday and rats on Friday. Twenty-four hours prior to sacrifice each animal received an identical dose of BA in corn oil, except that it contained benzyl acetate-ring ^{14}C as described above, and the animals were placed immediately in individual metabolism cages. For studies of dermal absorption rats were anesthetized with pentobarbital, hair was clipped from the intrascapular area of the back with surgical clippers and an area of 2 cm^2 was marked off with a fine tip marker. BA doses of 0.1, 1.0 or 10.0 mg containing 3.5 μCi benzyl acetate-ring ^{14}C were prepared in ethanol and applied to 2 cm^2 of skin in a total volume of 50 μl. The area of application was immediately covered with a perforated stainless steel shield secured with cyanoacrylate glue and each rat was placed in an individual metabolism cage.

Collection and Analysis of Biological Samples: Urine and feces were collected separately over a period of 24 hr. CO_2 and volatiles were collected by pulling air through the metabolism cages at 300-400 ml/min and then through a series of traps. Volatiles were collected in a series of two traps containing 200 ml cold ethanol. CO_2 was collected in a series of two traps containing 200 ml ethanolamine: methyl cellosolve (7:3). Traps were changed at 2, 4, 5 and 24 hr. Each animal was sacrificed 24 hr after treatment. At sacrifice, blood, liver, muscle, adipose, skin, lung, kidney, stomach and the site of application (tail for iv, skin for dermal) were collected from each animal. BA-derived ^{14}C in urine and the volatile and CO_2 trapping solutions were determined by counting triplicate samples in a Beckman Model LS-9800 Liquid Scintillation Counter (Beckman Instrument Co., Fullerton, CA). BA-derived ^{14}C in feces and tissues was determined by combustion of triplicate 100 mg samples to $^{14}CO_2$ in a Packard Tri-Carb Sample Oxidizer (Packard Instrument Co., Downers Grove, IL) and quantitation of the ^{14}C by liquid scintillation counting. No corrections were made in any data to account for recovery of radioactivity administered.

High-performance liquid chromatographic analysis was performed with Waters Associates, Inc. (Milford, MA) equipment using a 250mm x 4.6mm Rainin microsorb C-18 column. An 18-min linear solvent gradient of 100% to 25% 0.01M phosphate buffer, pH 7.9, with acetonitrile was used at a flow rate of 1.5 ml/min. Under these conditions, the following retention times were observed: benzoic acid, 1.6 min (unretained); hippuric acid, 6.3 min; S-benzyl mercapturic acid, 8.8 min; benzyl alcohol, 10.5 min and benzyl acetate, 15.8 min.

The S-benzyl mercapturic acid was prepared by stirring a mixture of 900 μl of benzyl chloride, 1 g of N-acetylcysteine, 1 g of sodium bicarbonate, 2 ml of water, and 2 ml of ethanol under nitrogen overnight. The mixture was then extracted with 50 ml of ether; the aqueous phase was acidified to pH 2 and extracted with 100 ml of ether. The second ether extract was concentrated to about 30 ml under vacuum. The mercapturic acid crystallized out on standing at 0°C overnight. The product was characterized by ^{1}H nmr.

RESULTS AND DISCUSSION

The clearance of benzyl acetate (BA) 24 hr following iv or oral dosing is presented in Table H1. Elimination of BA as CO_2 or volatiles was minimal following iv administration and was not determined following oral dosing because of the extra labor required. The lack of an effect of dose or route of administration on elimination in urine and feces indicates that absorption following oral administration was nearly complete and was not affected by dose. In every case except one, total recovery exceeded 90% of the dose administered. The one exception is believed to be an artifact, or possibly an error in dose preparation or in recovery and analysis of urine, and not due to slower elimination of BA when administered by gavage at 5 mg/kg. The data in Table H1 also indicate that clearance of BA in urine and feces did not change with repeat dosing at 500 mg/kg for 14 days.

A series of tissues was also analyzed for BA-derived radioactivity. The analysis of blood, liver, muscle, adipose, skin, lung, kidney and stomachs of animals that received either oral or iv doses did not indicate the presence of any BA-derived radioactivity. The detection limit for the 5 mg/kg dose was approximately 1 ppm. Such complete clearance of a xenobiotic from all major tissues in 24 hr is quite unusual. (In our experience, this is the most complete clearance of a xenobiotic we have ever witnessed.) Based on these results, it is believed that failure to find less than 100% of the total dose in excreta collected from rats treated with BA is more likely to be due to minor errors in dosing or collection of radioactivity than to retention of this compound or its metabolites in the tissues.

Clearance of BA by mice is described in Table H2. As was seen for the rat, absorption of BA from the gastrointestinal tract by mice was nearly complete and elimination of BA-derived radioactivity was rapid. Recovery of the 10 mg/kg iv and oral doses was poor, but an analysis of tissues from these animals did not reveal any trace of BA-derived radioactivity. The detection limit for BA-derived radioactivity in mouse tissue was approximately 0.1 ppm. It is believed that the poor recovery of BA in these studies was due to incomplete recovery of urine. Recovery of the 100 and 1,000 mg/kg and repeat oral doses was good and no apparent effect of the size or number of doses was observed.

Dermal absorption of BA was studied by applying a range of doses to a fixed area of skin on rats. Following application the rats were placed immediately in individual glass metabolism cages, which permitted the capture of all volatiles as well as urine and feces. At the end of 24 hr, treated rats were removed from the cages and sacrificed; the major tissues plus skin from the site of BA application were taken for analysis. The results of these studies are presented in Table H3, and data obtained from the study of BA clearance following iv dosing is presented for comparison. The major clearance of BA applied to skin was by volatilization. Loss to volatilization following iv dosing was minimal. It also appears that loss to volatilization was inversely correlated with dose. That is, as the dose increased loss to volatilization decreased and excretion in urine increased. This may have been due at least in part to the fact that the larger dose took longer to evaporate and therefore had more time to be absorbed through the skin. The decreased rate of evaporation was visibly apparent with the 10 mg dose and the spreading of this dose prevented the fixing of the stainless steel shield which was used with the two lower doses. The absence of the shield appeared to decrease retention at the application site, but increased excretion in feces and urine. These observations may also indicate that a portion of the dose was removed by grooming and subsequent ingestion. Elimination in CO_2 appears to be greater following dermal application, but this is more likely the result of a small spillover into the CO_2 trap from the volatile trap. Due to the very large dilution of BA or CO_2 in these traps, it was not practical to determine the nature of the volatile radioactivity.

It is apparent from the data in Table H3 that dermal absorption of BA was incomplete. However, dermal absorption may be estimated by the following formula:

$$\% \text{ Dermal Absorption} = \frac{\% \text{ Total Dose in Urine Following Dermal Application} \times 100}{\% \text{ Total Dose in Urine Following IV Injection}}$$

Calculations using this formula indicate dermal absorption of the 0.1, 1.0 and 10.0 mg over 2 cm^2 doses was approximately 14%, 19%, and 33% of the respective doses. However, as pointed out earlier, a portion of the 10 mg dose may have been ingested. In any case, results presented in Tables H1 and H3 indicate that it is not likely that a dose can be absorbed through the skin similar to that achieved by oral administration.

TABLE H1. BENZYL ACETATE CLEARANCE *(a)*—RAT

Dose Route	Dose (mg/kg)	Average % Total Dose ± SD			
		Urine	Feces	CO2	Volatile
IV	5 *(b)*	85.5 ± 4.81	1.81 ± 1.69	0.20 ± 0.5	2.54 ± 0.91
Oral	5 *(c)*	69.3 ± 6.7	1.31 ± 1.58		
Oral	50 *(c)*	94.5 ± 5.1	0.37 ± 0.25		
Oral	500 *(c)*	91.3 ± 6.5	0.98 ± 1.01		
Oral	500 x 14 *(d)*	91.0 ± 6.25	0.36 ± 0.57		

(a) % Total dose cleared in 24 hr by 3 rats at each dose ± SD.
(b) Intravenous injection into a tail vein.
(c) Oral gavage in 5 ml corn oil kg body wt.
(d) Repeat oral dose, 5 days wk for 14 days.

TABLE H2. BENZYL ACETATE CLEARANCE *(a)* - MOUSE

Dose Route	Dose (mg/kg)	Average % Total Dose ± SD	
		Urine	Feces
IV	10 *(b)*	62.3 ± 3.0	0.43 ± 0.38
Oral	10 *(c)*	63.0 ± 4.7	0.52 ± 0.33
Oral	100 *(c)*	89.0 ± 11.8	0.58 ± 0.58
Oral	1000 *(c)*	95.4 ± 3.6	0.70 ± 0.20
Oral	1000 x 14 *(d)*	88.3 ± 6.3	0.26 ± 0.06

(a) % Total dose cleared in 24 hr by 3 mice at each dose ± SD.
(b) Intravenous injection into a tail vein.
(c) Oral gavage in 10 ml corn oil/kg body wt.
(d) Repeat oral dose, 5 days/wk for 14 days.

TABLE H3. BENZYL ACETATE CLEARANCE FOLLOWING DERMAL APPLICATION *(a),(b)*

Dose Route	Dose (mg/2 cm²)	Average % Total Dose ± SD				Application Site *(c)*
		Urine	Feces	CO2	Volatile	
Dermal	0.1 *(d)*	11.6 ± 3.0	0.11 ± 0.05	2.56 ± 2.9	85.6 ± 8.1	1.44 ± 0.52
Dermal	1.0 *(d)*	16.1 ± 6.6	0.11 ± 0.02	1.85 ± 0.57	73.2 ± 9.0	0.66 ± 0.17
Dermal	10.0 *(e)*	28.3 ± 2.04	2.53 ± 2.04	0.88 ± 0.01	59.4 ± 8.6	0.03 ± 0.02
IV	5 mg *(f)*	85.5 ± 4.2	1.81 ± 1.7	0.2 ± 0.6	2.9 ± 0.91	--

(a) % Total dose cleared in 24 hr by 3 rats at each dose ± SD.
(b) Applied in a total volume of 50 µl ethanol solution to the intrascapular area of rats.
(c) % Total dose remaining in skin at site of application.
(d) Application site covered with a perforated stainless steel shield.
(e) Application site uncovered.
(f) Intravenous injection into a tail vein.

Since urine was the major route for clearance of absorbed BA, the urine from each animal used in this study was analyzed by HPLC for BA and its metabolites. Results obtained on HPLC analysis of urine from rats treated with BA are presented in Table H4. In these studies, benzyl acetate (Figure H1) was detected in trace quantities in the urine of only one rat. That rat had received a dermal dose and this trace of BA may represent contamination directly from the skin, but that cannot be confirmed. BA was not detected in the urine of mice (Table H5). The major metabolite of BA detected in all animals was hippuric acid (Tables H4 and H5, Figure H1). The identity of hippuric acid was confirmed by cochromatography with standard hippuric acid purchased commercially. This metabolite accounted for greater than 90% of the total radioactivity excreted in urine of all dose groups and its formation was apparently unaffected by dose, route or number of exposures. Hippuric acid is the anticipated metabolite formed by hydrolysis of the BA ester to benzyl alcohol and acetic acid, followed by oxidation of benzyl alcohol to benzoic acid and conjugation of benzoic acid with glycine. Hippuric acid is a natural constituent of human urine, but is more concentrated in the urine of herbivores. The formation of hippuric acid from benzoic acid was one of the first biotransformations of xenobiotic chemicals to be described.

Traces of benzyl alcohol were detected in the urine of some rats and mice (Tables H4 and H5, Figure H1). Its identity was confirmed by cochromatography with a synthetic standard. This metabolite is believed to represent a small portion of the total benzyl alcohol formed on hydrolysis of BA, which was excreted prior to oxidation to benzoic acid and conjugation with glycine to form hippuric acid. The possibility was considered that the presence of benzyl alcohol in urine might represent excretion of the parent compound in urine and subsequent breakdown prior to analysis. However, collection of urine over dry ice at 2-hr intervals and immediate HPLC analysis failed to show the presence of benzyl acetate, but did indicate the presence of benzyl alcohol.

The identity of the third metabolite of BA detected in urine of some rats and mice, benzyl mercapturic acid (Tables H4 and H5, Figure H1) was confirmed by synthesis of the authentic compound and cochromatography. This metabolite is the anticipated product of reaction of BA with glutathione catalyzed by glutathione-S-transferase and subsequent degradation of the glutathione conjugate to this mercapturic acid.

The "Other" metabolite(s) shown in Tables H4 and H5 represent one or occasionally two minor peaks observed in the HPLC analysis of rat and mouse urine. These peaks were not identified further than to confirm that they were quite polar relative to BA or the metabolites which were identified. This metabolite(s) was infrequently present in the urine of all animals of a given group and never accounted for a major portion of the dose.

CONCLUSION

Both rats and mice apparently have a considerable capacity to absorb BA from the gastrointestinal tract and metabolize it to hippuric acid and several minor metabolites, which are excreted in the urine. The relative amounts of the dose absorbed, metabolized, and excreted as the various metabolites were apparently unaffected by the size or number of doses administered. There was no evidence to indicate any saturation of this capacity in either species in the dose ranges studied, 5-500 mg/kg for rats, 10-1,000 mg/kg for mice. Therefore, it must be assumed that the innate capacity of these strains of rats and mice to metabolize and excrete BA is sufficient to handle the doses administered in the NTP 2-year studies of toxicity and carcinogenicity. Further, the data indicate that this innate capacity to absorb, metabolize, and excrete BA is not measurably altered by repeat administration of the doses used in the two-year assay for chronic toxicity and carcinogenicity.

Studies of dermal absorption, metabolism, and clearance indicate that BA is incompletely absorbed from the skin. Most of the dermal dose was lost to volatilization and a very minor portion of the dose remained at the site of application after 24 hr. That portion of the dose which was absorbed was apparently rapidly metabolized and excreted in the same manner as an oral dose. It is unlikely that it will be possible to saturate metabolism and clearance by BA by dermal application to rats and mice. These data indicate that the only effects of BA which could be demonstrated by skin paint studies which could not be achieved by oral administration would be those produced by direct contact with this chemical.

TABLE H4. BENZYL ACETATE METABOLITES IN RAT URINE *(a)*

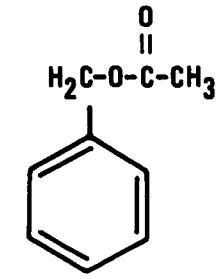
Dose Route	Dose (mg/kg)	% Total Dose In Urine	Benzyl Acetate	Hippuric Acid	Benzyl Alcohol	Mercapturic Acid	Other
IV	5	85.0	--	90.9 ± 4.3	4.1 *(b)*	5.2 ± 2.5	7.2 *(b)*
Oral	5	69.3	--	98.9 ± 1.9	--	3.2 *(b)*	--
Oral	50	94.5	--	97.0 ± 0.2	--	2.9 ± 0.2	--
Oral	500	91.3	--	94.6 ± 1.0	--	2.5 *(b)*	3.6 *(b)*
Oral	500 x 14	91.0	--	96.2 ± 3.4	--	3.1 *(b)*	2.2 *(b)*
Dermal	0.1	11.6	--	94.8 ± 1.0	1.4 *(b)*	4.6 ± 0.4	--
Dermal	1.0	16.1	0.4 *(b)*	95.3 ± 0.3	0.45 *(b)*	4.0 ± 0.6	0.2 *(b)*
Dermal	10.0	24.3	--	92.9 ± 4.1	2.4 ± 2.9	4.4 ± 1.0	0.5 *(b)*

(a) Average values obtained with 3 rats at each dose.
(b) Not found in all animals.

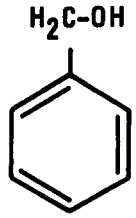
TABLE H5. BENZYL ACETATE METABOLITES IN MOUSE URINE *(a)*

Dose Route	Dose (mg/kg)	% Total Dose In Urine	Benzyl Acetate	Hippuric Acid	Benzyl Alcohol	Mercapturic Acid	Other
IV	10	62.3	--	98.7 ± 0.2	--	--	1.6 ± 0.2
Oral	10	63.0	--	93.9 ± 7.1	--	1.1 *(b)*	5.6 ± 6.5
Oral	100	89.0	--	99.3 ± 0.2	0.6 *(b)*	0.7 *(b)*	0.3 *(b)*
Oral	1000	95.4	--	97.9 ± 0.2	--	--	1.9 *(b)*
Oral	1000 x 14	88.3	--	97.6 ± 2.6	0.6 *(b)*	--	3.2 *(b)*

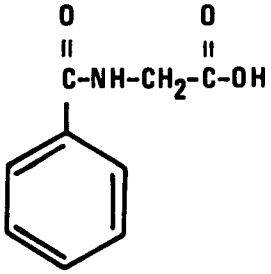
(a) Average values obtained with 3 mice at each dose.
(b) Not found in all animals.



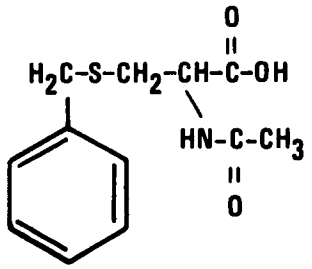
Benzyl Acetate



Benzyl Alcohol



Hippuric Acid



Benzyl Mercapturic Acid

Figure H1. Benzyl Acetate and Its Metabolites

APPENDIX I
ANALYSIS OF BENZYL ACETATE
MIDWEST RESEARCH INSTITUTE

APPENDIX I

A. ELEMENTAL ANALYSIS

Element	C	H
Theory	71.98	6.71
Lot 9640	71.36	6.74
	71.55	6.90
Lot 4821	71.59	6.60
	71.34	6.72
Lot 12952	72.46	6.62

(Average of two values)

B. WATER ANALYSIS (Karl Fischer)

Lot 9640: $0.07 \pm 0.01(\delta)\%$

Lot 4821: $0.21 \pm 0.007(\delta)\%$

Lot 12952: $0.11 \pm 0.001(\delta)\%$

C. TITRATION

1. Ester Value

(Hydrolysis and back titration, ASTM, 1974).

Benzyl acetate (1 ml) was hydrolyzed for 2 hours and 4 hours at room temperature with 20.0 ml 1.0 N aqueous potassium hydroxide in 25 ml isopropanol. The excess base was back titrated with 1N H_2SO_4. Since no significant difference was found in the volume of sulfuric acid needed to titrate the excess potassium hydroxide after 2 hours and 4 hours, the reaction was considered complete after 2 hours, and all values were averaged together to give the reported results:

Lot 9640: $96.0 \pm 0.8(\delta)\%$

Lot 4821: $99.1 \pm 0.4(\delta)\%$

Lot 12952: $101.3 \pm 0.8(\delta)\%$

2. Free Acid

(Titration with 0.1 N sodium hydroxide)

All Lots: $<0.1\%$ acidity (assumed to be acetic acid)

D. BOILING POINT

	Determined	Literature Value
Lot 9640	213° ± 1(δ)°C at 731 torr (visual, micro boiling point) 215°C with endotherms at 213°C and 214°C (Dupont 900 DTA)	b.p.: 208°-215°C at 760 torr (Joski and Merchant, 1955)

E. INDEX OF REFRACTION

Lot 9640: n_D^{20} : $1.5020 \pm 0.0001(\delta)$ — n_D^{20} : 1.5232 (Merck, 1976)

F. DENSITY

Lot 9640: d_{22}^{24} : $1.0526 \pm 0.0001(\delta)$ g/ml — d_{22}^{24} : 1.050 g/ml (Merker and Scott, 1961)

APPENDIX I

G. THIN-LAYER CHROMATOGRAPHY

Plates: Silica gel 60-F254
Ref. Standard: Geranyl acetate
Visualization: Ultraviolet, 254 and 366 nm, and iodine vapor
Amount Spotted: 10 and 30 μl, 1% solution in methanol

	System 1: Benzene:1,4-Dioxane (85:15)	System 2: Methylene chloride, 100%
Lot 9640:	R_f: 0.83 (trace), 0.73 (major), origin (trace)	R_f: 0.89 (trace, 0.80 (slight trace), 0.49 (major), origin (trace)
	R_{st}: 1.1, 0.95, origin	R_{st}: 2.0, 1.8, 1.1, origin
Lot 4821:	R_f: 0.83	R_f: 0.60
	R_{st}: 0.90	R_{st}: 0.99
Lot 12952:	R_f: 0.85	R_f: 0.52
	R_{st}: 0.95	R_{st}: 0.98

H. VAPOR-PHASE CHROMATOGRAPHY

1. Lot 9640

Instrument: Tracor MT 220
Detector: Flame ionization
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

a. System 1

Column: 10% SP-2330 on 100/120 mesh Chromosorb W(AW), 1.8 m x 4 mm I.D. glass
Oven temperature program: 100°C, 10 min; 100°-250°C at 10°C/min
Inlet temperature: 165°C
Detector temperature: 205°C
Sample injected: 6 μl of a 1% solution in methanol to detect impurities; 6 μl of a 0.5% solution in methanol to check for overloading.
Results: Major peak and four impurities. All impurities observed were shoulders on the falling edge of the major peak or on the baseline rise in the temperature program. The areas of the impurities total <1% of the area of the major peak.

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	13.4	1.00	100
2	14.3	1.07	shoulder 0.1-0.5
3	14.6	1.09	shoulder 0.1-0.5
4	15.7	1.17	shoulder <0.03
5	16.4	1.22	shoulder <0.05

b. System 2

Column: 3% SP-2250 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 80°C, 10 min; 80°-250°C at 10°C min
Inlet temperature: 80°C
Detector temperature: 270°C
Sample injected: 5 μl of a 0.5% solution in hexane
Results: Major peak and three impurities. The areas of the impurities total <1% of the major peak.

APPENDIX I

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	7.5	1.0	100
2	12.9	1.7	0.3
3	13.9	1.9	0.01
4	14.8	2.0	0.09

2. Lot 4821

Instrument: Varian 3740
Detector: Flame ionization
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

a. System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW); 1.8 m x 4 mm I.D., glass
Oven temperature program: 80°C, 10 min; 5 min; 80° to 200°C at 10°C/min
Inlet temperature: 170°C
Detector temperature: 210°C
Sample injected: 4 μl of a 1% solution in methanol to detect impurities; 4 μl of a 0.5% solution to check for overloading
Results: Major peak and six impurities; two peaks subsequent to the major peak had areas of 0.52% and 0.22%; the other four, two prior to and two subsequent to the major peak, had total areas <0.1% of the major peak.

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	7.8	0.57	0.02
2	10.9	0.80	0.04
3	13.7	1.00	100
4	14.5	1.06	0.02
5	14.9	1.09	0.01
6	15.3	1.12	0.52
7	15.8	1.15	0.22

b. System 2

Column: 3% OV-17 on 80 100 Supelcoport; 1.8 m x 4 mm I.D. glass
Oven temperature program: 80°C, 10 min; 80°-250°C at 10°C min
Inlet temperature: 200°C
Detector temperature: 270°C
Sample injected: 5 μl of a 1% solution in hexanes to detect impurities; 5 μl of a 0.5% solution in hexanes to check for overloading.
Results: Major peak and one impurity.

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	12.8	1.00	100
2	18.3	1.43	0.29

Note: OV-17, used in this analysis, is very similar to SP-2250, which was used for the analysis of the other two lots, in chemical composition and chromatographic characteristics such as McReynold's constants and resolution, but it is supposed to be more thermally stable so that it gives less baseline rise in a temperature program.

APPENDIX I

3. Lot 12952 Instrument: Varian 3700
Detector: Flame ionization
Inlet Temperature: 100°C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

a. System 1

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m x 4 mm I.D., silylated glass
Detector Temperature: 250°C
Oven temperature program: 60°C, initial hold for 5 min, followed by a 10°C/min program to 200°C; and isothermal at 170°C for 1% area determination
Sample injected: 1.5 µl of neat compound to detect impurities and 3 µl of 1.0 and 0.5 (v/v)% solutions in hexanes to determine linearity of detector response and major peak area
Results: A major peak, followed by two impurities with individual relative areas greater than 0.1% and one impurity with a relative area less than 0.1% was detected.

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	16.9	1.00	100.0
2	18.6	1.10	0.6
3	19.2	1.14	0.3

b. System 2

Column: 3% SP2250 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., silylated glass
Detector temperature: 270°C
Oven temperature program: Initial 5 min hold at 50°C followed by a 10°C/min program to 250°C for impurity detection; isothermal at 120°C for 1% area determination
Sample injected: 1.5 µl of neat compound to detect impurities and 3 µl of 1.0 and 0.5 (v/v)% solutions in hexanes to determine linearity of detector response and major peak area
Results: A major peak, preceded by one and followed by two impurities, was detected. Only one of the two impurities following the major peak had a relative area of greater than 0.1%.

Peak	Retention Time (min)	Retention Time (Relative to Benzyl Acetate)	Area (Percent of Benzyl Acetate)
1	11.3	0.88	0.4
2	12.9	1.00	100.0
3	16.8	1.30	0.2

APPENDIX I

I. SPECTRAL DATA

1. Infrared

Lot 9640	Instrument: Beckman IR-12 Cell: 0.013 mm liquid cell with sodium chloride windows Results: See Figure 5	Spectra of all batches consistent with literature spectrum (Pouchert, 1975) Peaks consistent with those listed in literature (Chattopadhyay and Mukherjee, 1966)
Lot 4821	Instrument: Beckman IR-12 Cell: Liquid between silver chloride plates Results: See Figure 6	
Lot 12952	Instrument: Perkin-Elmer 283 Cell: Thin film between silver chloride plates Results: See Figure 7	

2. Ultraviolet/Visible

Instrument: Cary 118

a. Lot 9640

Determined λ max (nm)	ε x 10	Literature Value (Bag, 1968) λ max (nm)
269	10.2 ± 0.2 (δ)	268
264	16.4 ± 0.3 (δ)	264
262	15.8 ± 0.3 (δ)	262
258	20.2 ± 0.3 (δ)	256 (shoulder)
252	15.7 ± 0.3 (δ)	252
248 (shoulder)	11.3 ± 0.2 (δ)	248
243 (shoulder)	7.8 ± 0.2 (δ)	246
237 (shoulder)	5.1 ± 0.3 (δ)	

No absorbance between 350 and 800 nm (visible range) at a concentration of 0.5 mg/ml.
Solvent Methanol

Solvent: Ethyl alcohol

b. Lot 4821

Determined λ max (nm)	ε x 10	Literature Value (Bag, 1968) λ max (nm)
267.5	9.39 ± 0.06 (δ)	268
263.1	15.64 ± 0.16 (δ)	264
257.6	19.09 ± 0.20 (δ)	262
252	15.11 ± 0.08 (δ)	256 (shoulder)
248 (shoulder)	10.99 ± 0.01 (δ)	252
243 (shoulder)	7.59 ± 0.07 (δ)	248
		246

No absorbance between 350 and 800 nm (visible range at a concentration of 0.57 mg/ml.
Solvent: 95% Ethanol

Solvent: Ethyl alcohol

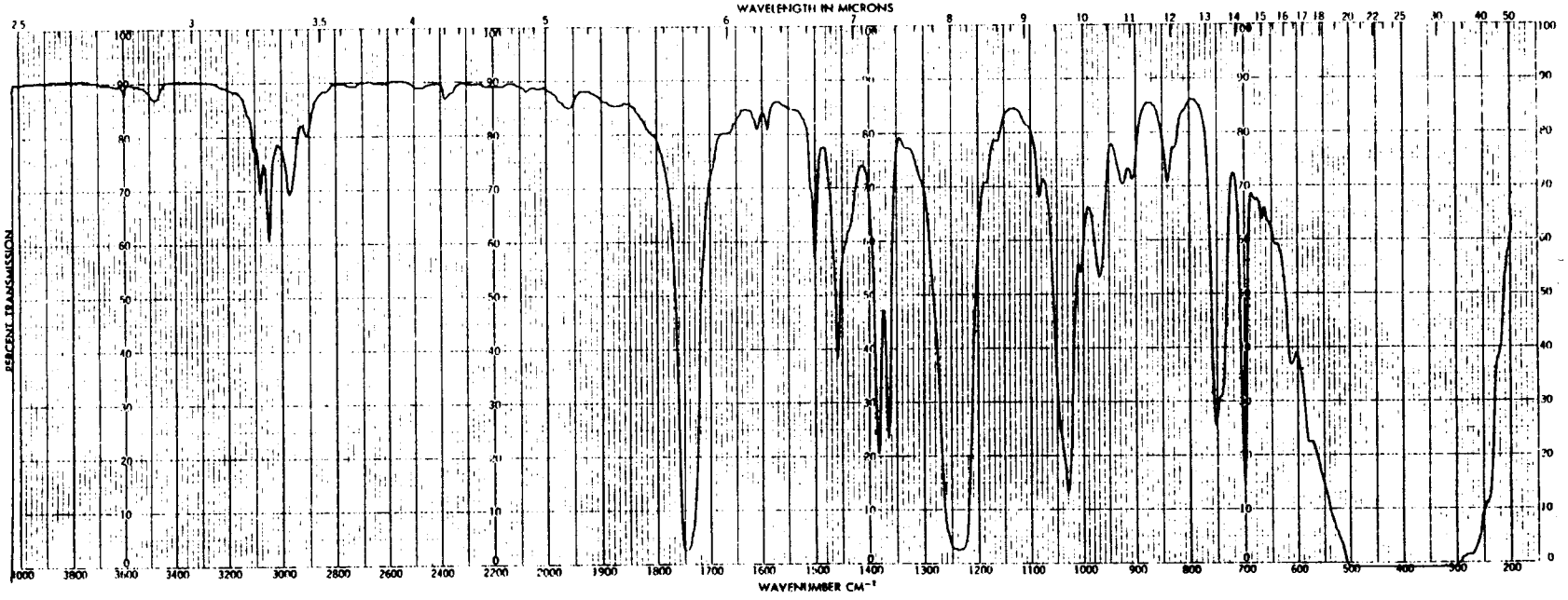


Figure 5. Infrared Absorption Spectrum of Benzyl Acetate (Lot No. 9640)

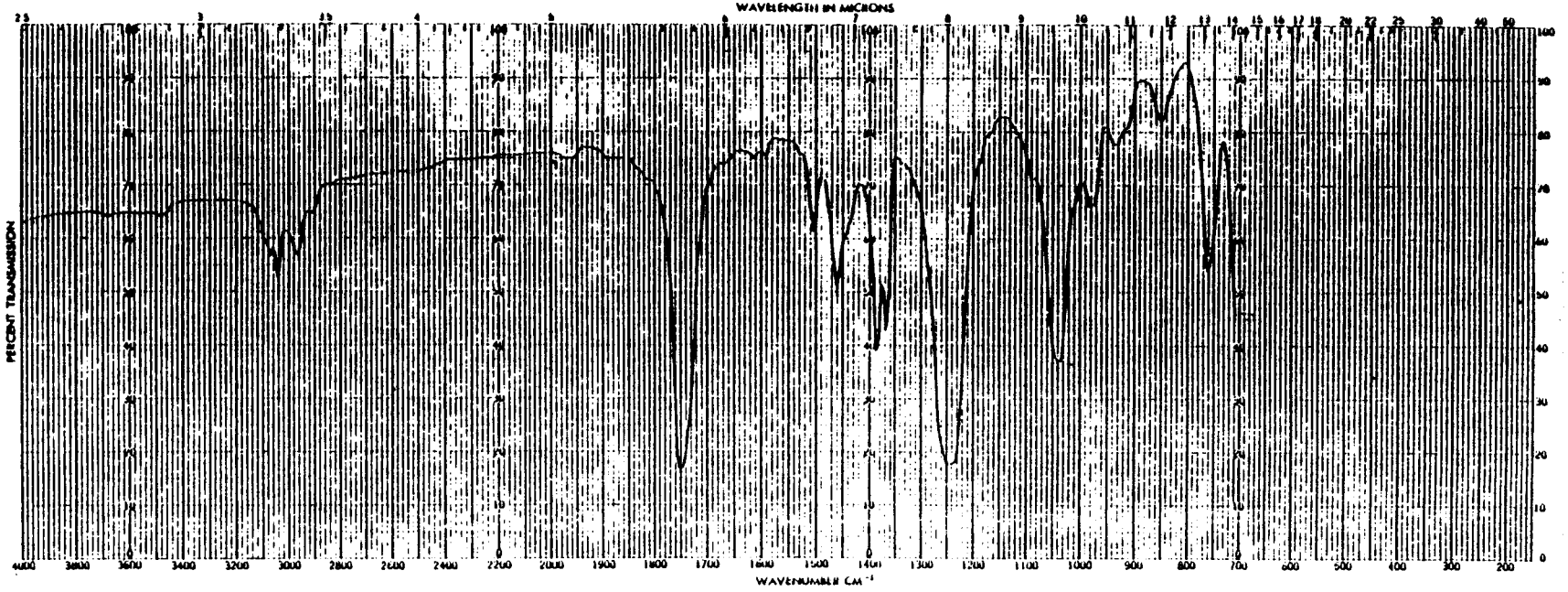


Figure 6. Infrared Absorption Spectrum of Benzyl Acetate (Lot No. 4821)

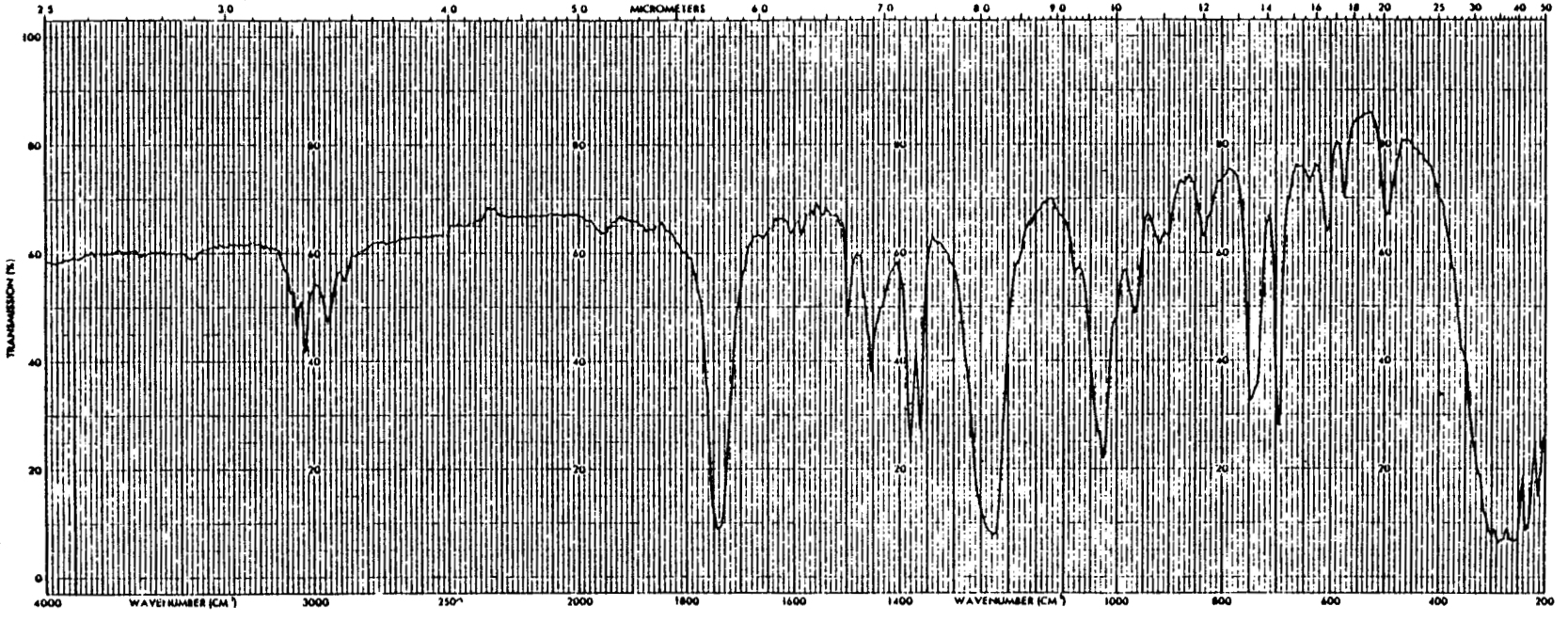


Figure 7. Infrared Absorption Spectrum of Benzyl Acetate (Lot No. 12952)

c. Lot 12952

Determined λ max (nm)	ε x 10	Literature Value λ max (nm)	ε x 10
267	10.12 ± 0.24 (δ)	267	9.00
263	16.54 ± 0.24 (δ)	263	15.85
257.5	20.22 ± 0.26 (δ)	257	19.74
252	15.14 ± 0.24 (δ)	252	14.68

Shoulders were also observed at 262, 247.5, 242, and 237 nm
Solvent: 95% Ethanol

Solvent: Cyclohexane

3. Nuclear Magnetic Resonance

a. Lot 9640

Determined

Instrument: Varian HA-100
Solvent: Neat, tetramethylsilane added as internal standard
Assignments: Figure 8
(a) s, δ 1.81 ppm;
(b) s, δ 4.93 ppm;
(c) m, δ 7.15 ppm
Integration Ratios:
(a) 2.79
(b) 2.03
(c) 5.18

Literature Values

(a) ν 121.8 (Arakana and Hashimoto, 1968)
δ 2.03 ppm
(b) ν 301.5
δ 5.02 ppm
Solvent: Carbon tetrachloride

b. Lot 4821

Instrument: Varian EM-360A
Solvent: Chloroform-d, with added tetramethylsilane as internal standard
Assignments: Figure 9
(a) s, δ 2.04 ppm;
(b) s, δ 5.04 ppm;
(c) m, δ 7.28 ppm
Integration ratios:
(a) 2.88
(b) 2.07
(c) 5.00

(a) ν 121.8 (Arakana and Hashimoto, 1968)
δ 2.03 ppm

(b) ν 301.5
δ 5.02 ppm
Solvent: Carbon tetrachloride

c. Lot 12952

Instrument: Varian EM-360A
Solvent: Chloroform-d, with added tetramethylsilane internal standard
Assignments: Figure 10
(a) s, δ 2.1 ppm;
(b) s, δ 5.08 ppm;
(c) m, δ 7.32 ppm
(d) Impurity
Integration ratios:
(a) 2.9
(b) 2.1
(c) 5.0

Consistent with literature spectrum (Sadtler Standard Spectra) and with spectra of other lots

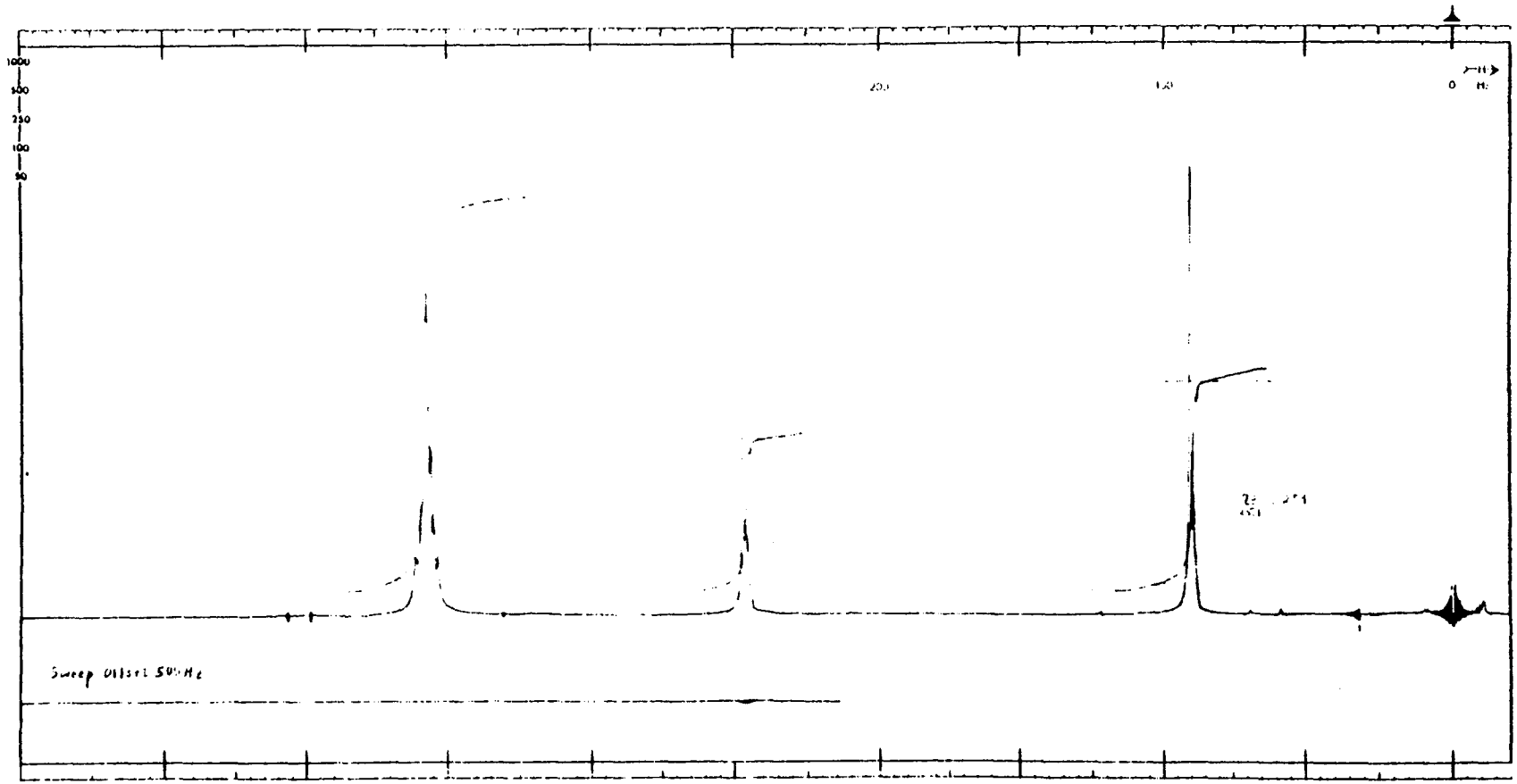


Figure 8. Nuclear Magnetic Resonance Spectrum of Benzyl Acetate (Lot No. 9640)

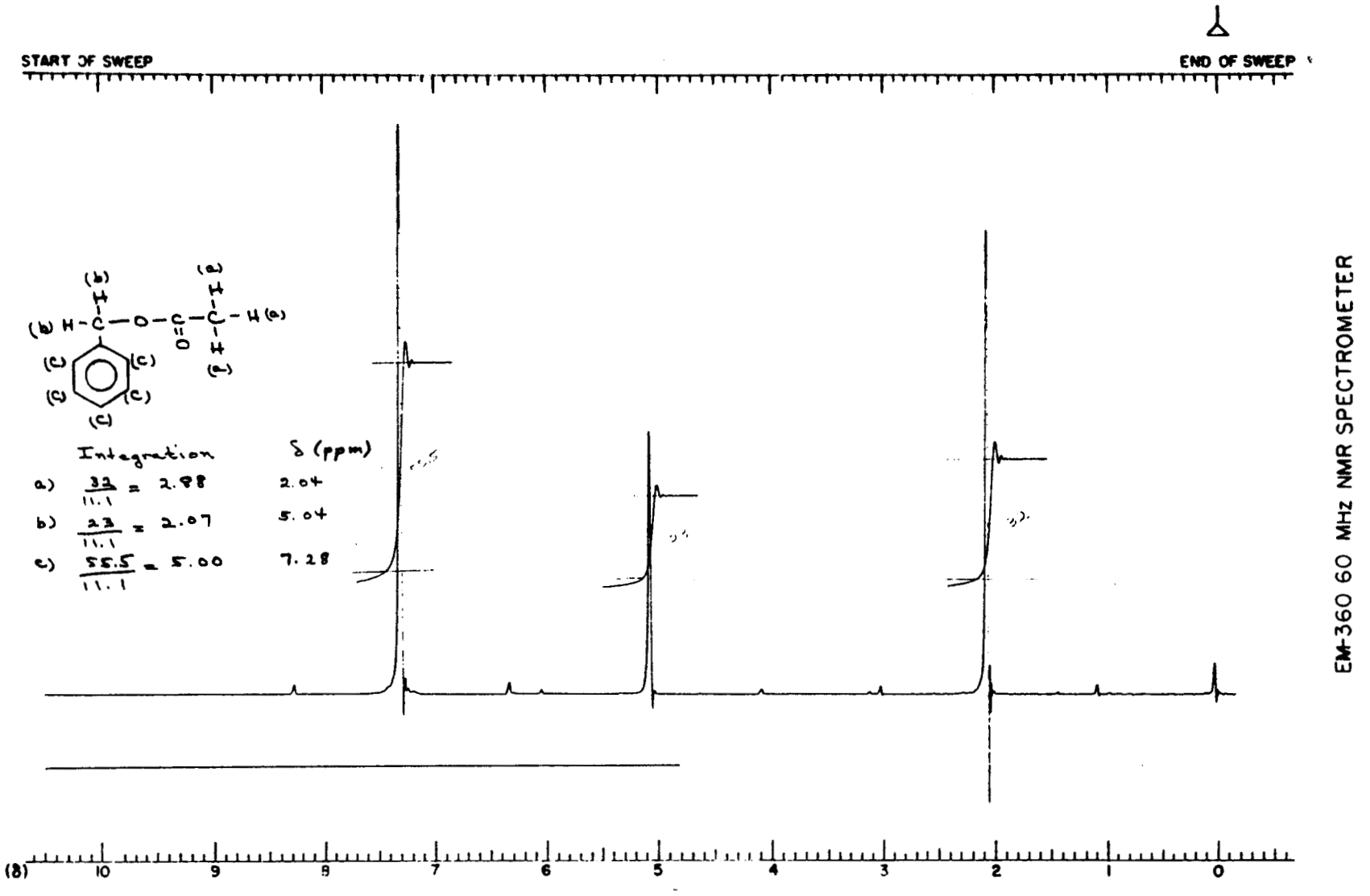


Figure 9. Nuclear Magnetic Resonance Spectrum of Benzyl Acetate (Lot No. 4821)

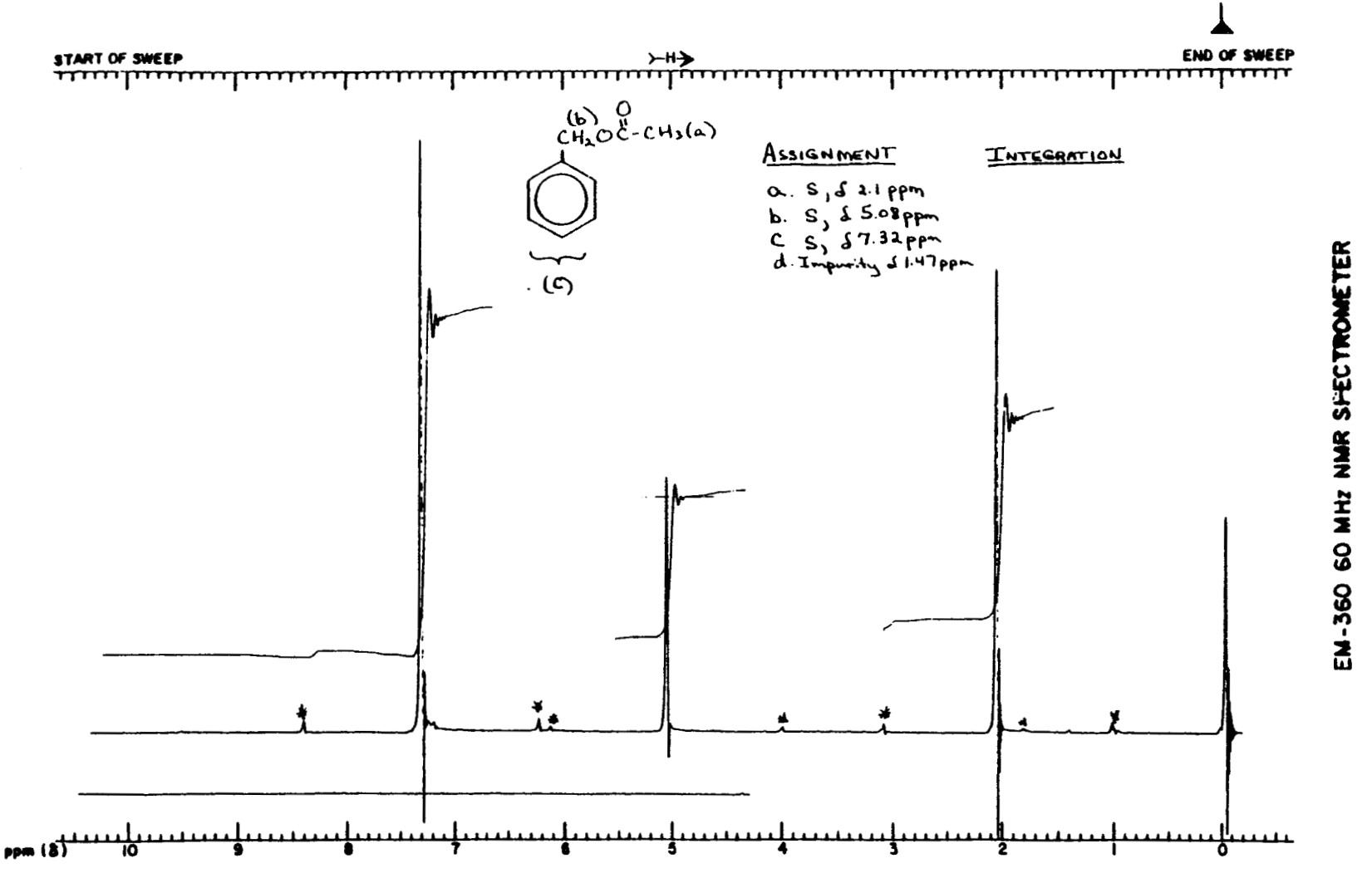


Figure 10. Nuclear Magnetic Resonance Spectrum of Benzyl Acetate (Lot No. 12952)

APPENDIX J
SUPPLEMENTARY REPORT
FCC ANALYSIS OF BENZYL ACETATE
MIDWEST RESEARCH INSTITUTE

EXECUTIVE SUMMARY

Two lots of benzyl acetate, Lot Nos. 4821 and 12952, used previously for chronic bioassay, were found to meet the specifications given for benzyl acetate in the Food Chemicals Codex (FCC), Third Edition. The ester determination value met the minimum FCC requirement, but was greater than the generally specified maximum value.

SUPPLEMENTARY REPORT - FCC ANALYSIS OF BENZYL ACETATE

I. INTRODUCTION

The purpose of this work was to determine whether the two lots of benzyl acetate, Lot Nos. 4821 and 12952, used in the chronic phase of an NTP bioassay study, met FCC III specifications.[1]

II. FCC ANALYSIS

A. GAS-LIQUID CHROMATOGRAPHIC (GLC) PROFILE[2]

1. INSTRUMENTAL SYSTEM

Instrument: Varian Vista 6000
Detector: Flame ionization
Inlet Temperature: 200°C
Detector Temperature: 250°C
Carrier Gas: Nitrogen
Carrier Flow Rate: 40 cc/min
Column: 10% SP-2330 on 100/120 supelcoport; 1.8 m x 4 mm ID, glass
Oven Temperature Program: Programmed from 120 to 225°C at 4°C/min for impurity profile; isothermal at 140°C for major peak quantitation and to check for detector overloading
Samples Injected: Neat liquid to detect impurities; 1.0 and 0.5% (v/v) solutions (∿ 3 µl) in acetone to quantitate the major peak and check for detector overload

2. RESULTS*

a. Lot No. 4821: A major peak and one impurity with an area of 0.35% relative to the major peak area were detected. This impurity, which eluted after the major peak, was identified as benzyl alcohol by retention time matching.

Three additional impurities, two eluting before and one after the major peak, with areas less than 0.1% relative to the major peak were also seen. (See Figure 1 attached.)

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[1] Food Chemicals Codex, Third Edition, National Academy Press, Washington, D.C., p. 358-359 (1981).

[2] Ibid., p. 440.

* At the request of NTP, this system was used to check for the presence of benzyl chloride. Benzyl chloride was shown to have a retention time of 4.68 min on this system. No impurity was seen in either lot with that retention time. The approximate detection level for benzyl chloride was 0.05% by relative area.

Peak No.	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (% of Major Peak Area)
1	8.20	1.00	100.0
2	10.69	1.30	0.35

b. Lot No. 12952: A major peak and one impurity with an area of 0.34% relative to the major peak were detected. This impurity, which eluted after the major peak, was identified as benzyl alcohol by retention time matching.

Two additional impurities, one eluting before and one after the major peak, with areas less than 0.1% relative to the major peak were also seen. (See Figure 2, attached.)

Peak No.	Retention Time (min)	Retention Time (Relative to Major Peak)	Area (% of Major Peak Area)
1	8.20	1.00	100.0
2	10.69	1.30	0.34

3. CONFORMANCE TO SPECIFICATIONS

Both lots exhibited an impurity with a relative retention time corresponding to that given in the FCC for a typical lot of benzyl acetate. The relative area of this impurity was smaller than the relative area listed for a typical lot. Another impurity listed as usually present in a typical lot was absent in both lots analyzed.

B. INFRARED ABSORPTION SPECTRUM[3]

Instrument: Perkin-Elmer 283

1. METHOD

The samples were prepared as thin films between silver chloride plates.

2. RESULTS

The infrared absorption spectra of Lot Nos. 4821 and 12952 exhibited the same maxima as the FCC reference spectrum of benzyl acetate (see Figures 3 and 4).

3. CONFORMANCE TO SPECIFICATIONS

Both lots met the FCC requirements for this test. The FCC specifies that the infrared absorption spectrum of the sample shall exhibit maxima at the same wavelengths as those shown in the reference spectrum.

[3] Ibid., p. 617.

C. ESTER DETERMINATION ASSAY[4]

1. METHOD

Samples were hydrolyzed by refluxing with excess alcoholic potassium hydroxide on a steam bath for 1 hr. After cooling, the excess potassium hydroxide was back titrated with 0.5 N hydrochloric acid to the phenophthalein endpoint.

2. RESULTS

Lot No. 4821	102.9 ± 0.5(s)% (n = 3)
Lot No. 12952	103.3 ± 0.9(s)% (n = 3)

3. CONFORMANCE TO SPECIFICATIONS

Both lots met the minimum FCC requirements specified for benzyl acetate. However, the titration results were greater than the general specified maximum value of 100.5%.

D. ACID VALUE[5]

1. METHOD

Ten-gram samples of benzyl acetate were dissolved in 50 ml of neutralized ethanol. The samples were then titrated back to the phenolphthalein endpoint with 0.1 N aqueous sodium hydroxide.

2. RESULTS

Lot No.	Acid Value
4821	0.059 ± 0.001(s) (n = 2)
12952	0.060 ± 0.001(s) (n = 2)

3. CONFORMANCE TO SPECIFICATIONS

Both lots met FCC requirements for acid content. The FCC specifies that the acid value should not exceed 1.0.

E. REFRACTIVE INDEX DETERMINATION[6]

1. METHOD

The refractive indices of both lots were measured using an Abbé refractometer standardized at 1.500 with a certified index of refraction liquid.

[4] Ibid., p. 500-501.
[5] Ibid., p. 499.
[6] Ibid., p. 359.

2. RESULTS

Lot No.	R.I.
4821	1.501
12952	1.502

3. CONFORMANCE TO SPECIFICATIONS

Both lots met FCC requirements for refractive index determination. The FCC requires the observed refractive index to be between 1.501 and 1.504 at 20°C.

F. SOLUBILITY IN ALCOHOL[7]

1. METHOD

One milliliter of benzyl acetate sample was transferred to a 10-ml stoppered graduated cylinder (0.1 ml subdivisions). Small increments of 60% ethanol were added and the cylinder was thoroughly shaken after each addition. The temperature was maintained at 25°C for this test.

2. RESULTS

Lot No.	60% Ethanol Required to Obtain a Clear Solution (ml)
4821	5
12951	5

3. CONFORMANCE TO SPECIFICATIONS

Both lots met FCC requirements for solubility in alcohol. The FCC specifies that 1 ml of benzyl acetate must be soluble in not more than 5 ml of 60% ethanol.

G. SPECIFIC GRAVITY DETERMINATION[8]

1. METHOD

The density of each sample was determined at 25°C using a calibrated 5 ml pycnometer. The density of the sample was divided by the published density of water at 25°C to calculate the specific gravity.

2. RESULTS

Lot No.	Specific Gravity
4821	1.052 ± 0.001 (n = 4)
12951	1.052 ± 0.001 (n = 4)

[7] Ibid., p. 502.
[8] Ibid., p. 359.

3. CONFORMANCE TO SPECIFICATIONS

Both lots met FCC requirements for specific gravity. The FCC specifies that the specific gravity for benzyl acetate at 25°C shall lie between 1.052 and 1.056.

H. TEST FOR CHLORINATED COMPOUNDS[9]

1. METHOD

The sample was applied to a rolled portion of 20 mesh copper gauze per FCC instructions. The gauze was then held in the outer edge of a Bunsen flame adjusted to a height of 4 cm. The flame was then observed for any trace of green color.

2. RESULTS

Lot No.	Appearance of Green Color
4812	Negative
12952	Negative

3. CONFORMANCE TO SPECIFICATIONS

Both lots met FCC requirements for the chlorinated compounds test. The FCC specifies that not even a transient green color should be imparted to the flame in the test described above.

I. SUMMARY AND DISCUSSION

All tests listed in the third edition of the Food Chemicals Codex for benzyl acetate were performed on Lot Nos. 4821 and 12952. The results are tabulated below.

[9] Ibid., p. 500.

Test	Results		Specifications
	Lot No. 4821	Lot No. 12952	
1. GLC profile	Major peak with a later eluting impurity identified as benzyl alcohol by retention time matching. Impurity has an area of 0.35% relative to the major peak. Three additional impurities with relative areas less than 0.1% were also seen.	Major peak with a later eluting impurity identified as benzyl alcohol by retention time matching. Impurity has an area of 0.34% relative to the major peak. Two additional impurities with relative areas less than 0.1% were also seen.	Typical impurity profile by area: 98.2% benzyl acetate, 1.7% benzyl alcohol, and 0.1% of a later eluting, unidentified impurity.
2. Infrared absorption spectrum	Passes test	Passes test	IR absorption maxima for sample matches those of reference spectra.
3. Ester determination	102.9 ± 0.5(s)	103.3 ± 0.9(s)	98.0% minimum specified for benzyl acetate. 100.5% is a generally specified maximum.
4. Acid value	0.059 ± 0.001(s)	0.060 ± 0.001(s)	Less than 1.0
5. Refractive index	1.501	1.502	1.501-1.504
6. Solubility in alcohol	1 ml dissolved in 5 ml	1 ml dissolves in 5 ml	1 ml of benzyl acetate dissolve in ≦ 5 ml of 60% alcohol.
7. Specific gravity	1.052 ± 0.001	1.052 ± 0.001	1.052-1.056
8. Chlorinated compounds	Passes test	Passes test	No green color observed in flame test.

J. CONCLUSIONS

Both lots of benzyl acetate tested met the FCC specifications for benzyl acetate, although the ester determination value was greater than the generally specified maximum.

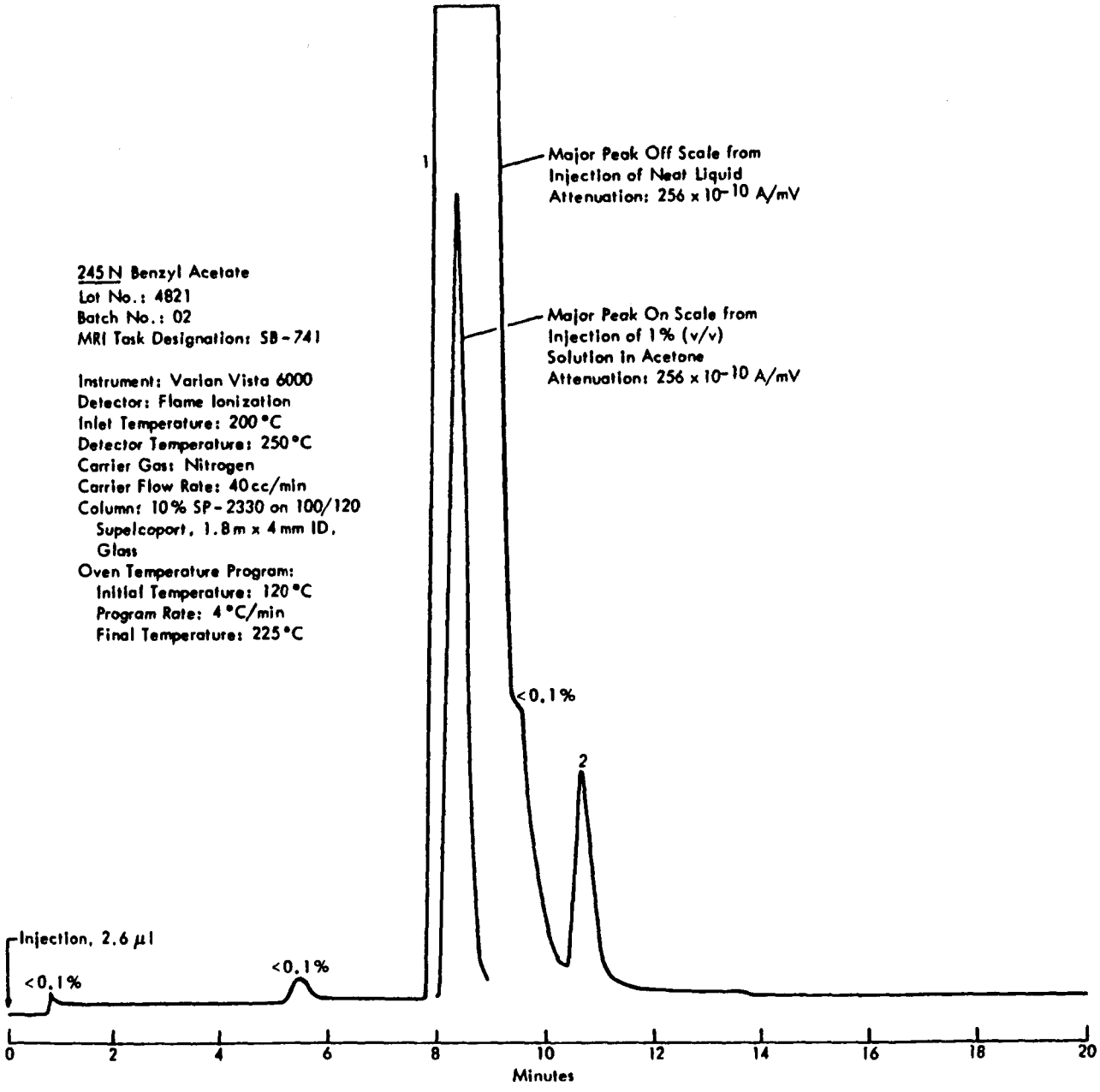

Figure 1 - Gas Chromatographic Impurity Profile of Bulk Chemical

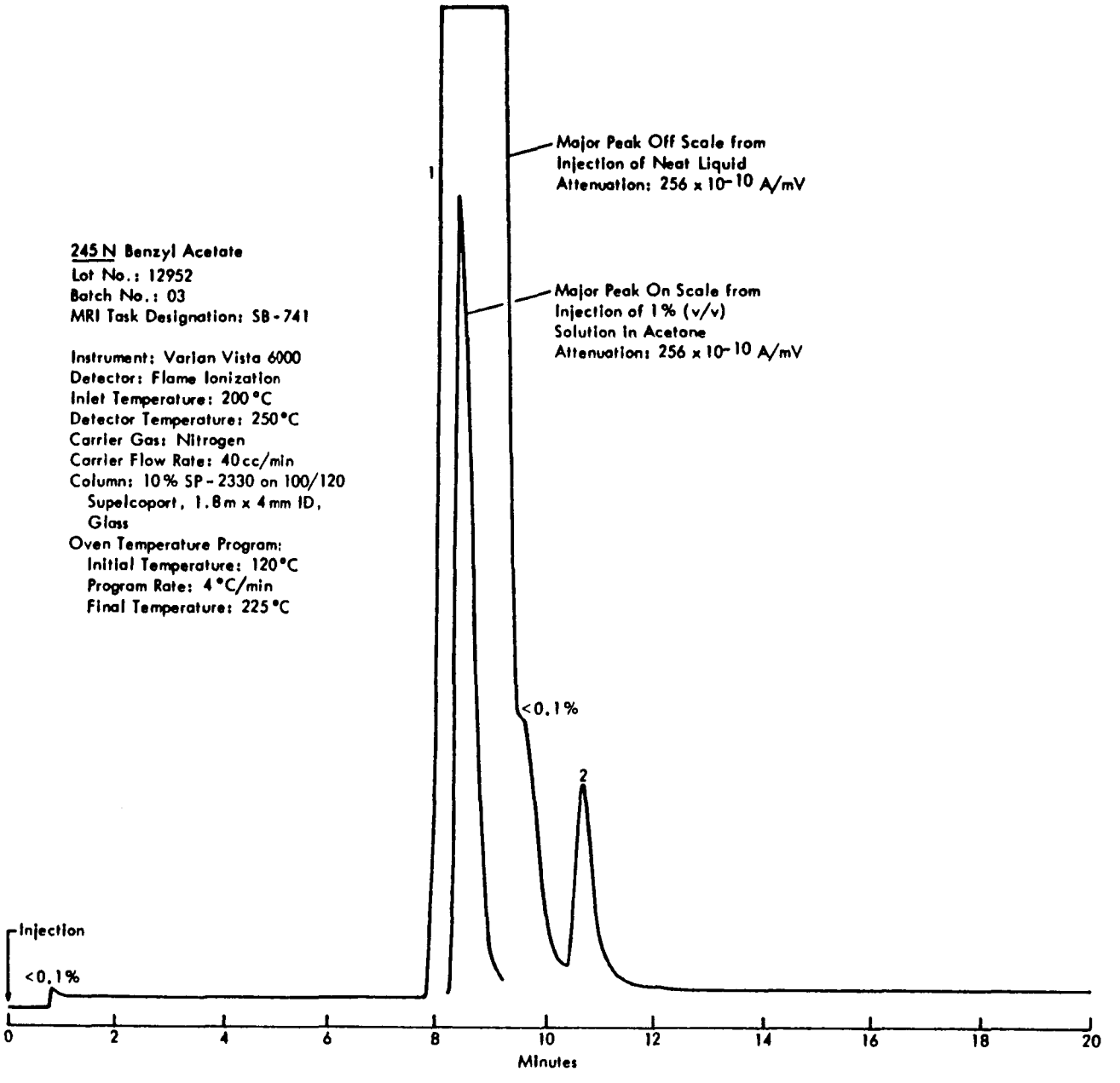

Figure 2 - Gas Chromatographic Impurity Profile of Bulk Chemical

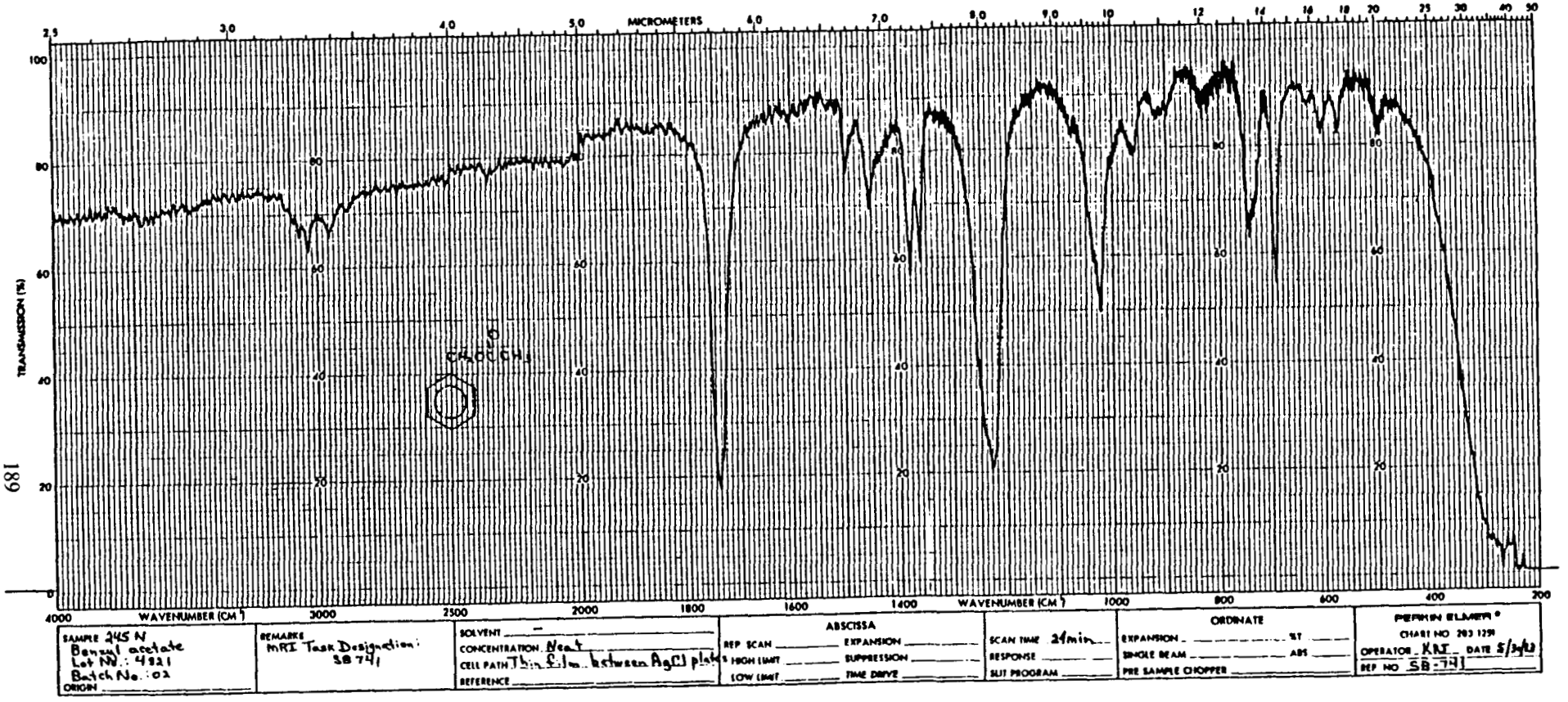

Figure 3 - Infrared Spectrum of Benzyl Acetate, Lot No. 4821, Batch No. 02, SB-741

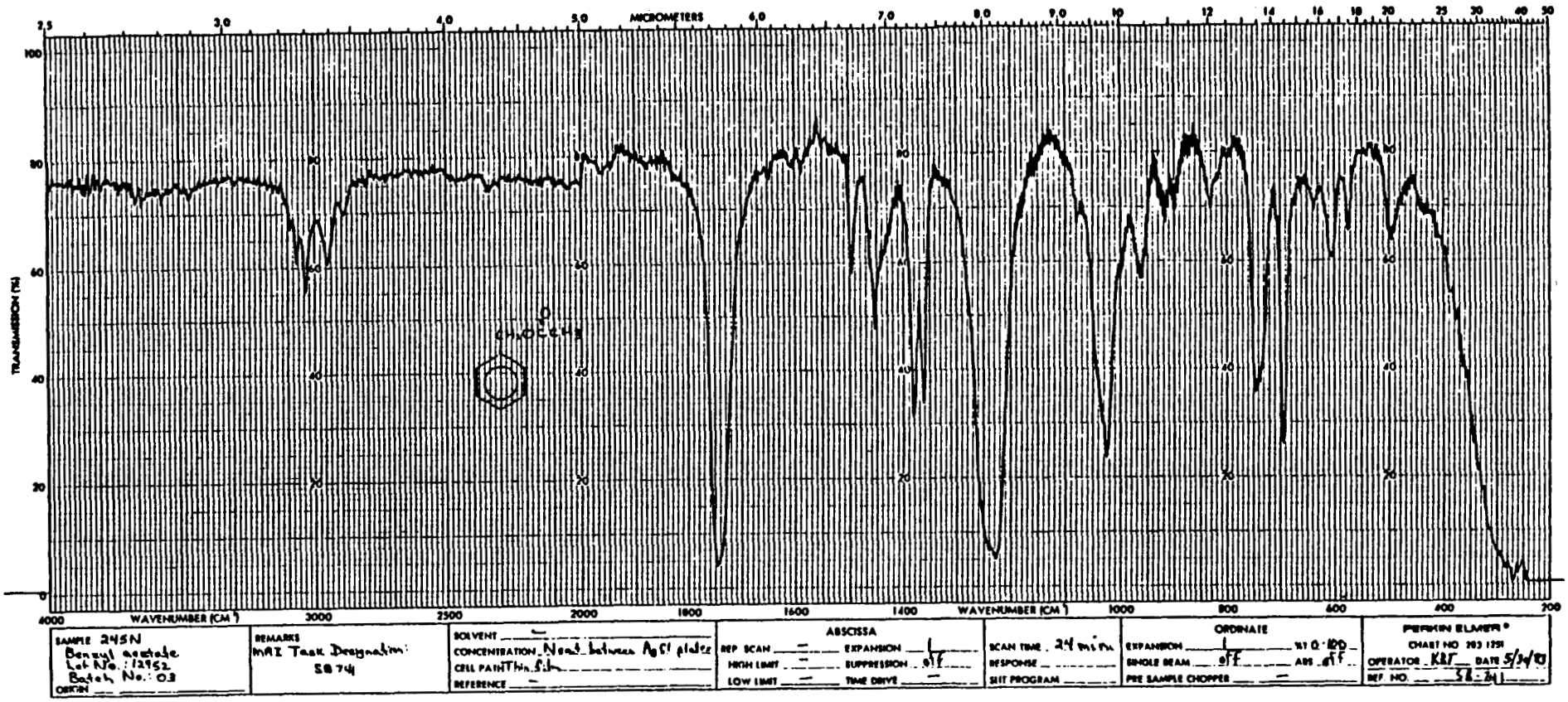

Figure 4 - Infrared Spectrum of Benzyl Acetate, Lot No. 12952, Batch No. 03, SB-741

APPENDIX K
ANALYSIS OF BENZYL ACETATE/CORN OIL MIXTURES FOR STABILITY OF BENZYL ACETATE

APPENDIX K

A. SAMPLE PREPARATION AND STORAGE

Solutions of benzyl acetate in corn oil (2.0% w/v) were prepared in duplicate for storage of 0, 1, 2, 4, and 7 days, respectively. A typical sample was prepared as follows: 2.00 ml of corn oil was transferred into an 8.5 ml-septum vial and the vial was sealed (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Bio-Medical Products, Inc.; aluminum crimp seals from Wheaton Scientific Company, Inc.) and weighed. Approximately 40 mg of benzyl acetate was then injected, and the vial was reweighed to determine the exact amount of benzyl acetate added. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature (25°C) for the appropriate time period.

B. EXTRACTION AND ANALYSIS

At the end of each storage period, the appropriate samples were extracted with 2.00 ml of methanol, which was injected into the vials with a 2-ml syringe. The two-phase mixtures were thoroughly shaken by hand and placed in an ultrasonic vibratory bath for 2 minutes. Aliquots for analysis were removed directly from the top (methanol) layer of each sample by microliter syringe and analyzed by the vapor-phase chromatographic system described below.

Instrument: Bendix 2500 with Hewlett-Packard 3380A Automatic Integrator
Column: 3% OV-17 on 80/100 mesh Chromosorb W (HP), 1.8 m x 2 mm I.D., glass
Detection: Flame ionization
Temperatures: Inlet, 140°C
Oven, 95°C, isothermal
Detector, 165°C
Carrier gas: Nitrogen; flow rate, 30 cc/min
Retention time of major component: 5.0 min

C. RESULTS

Storage Time (Days)	Average Percent Chemical Found in Chemical/Vehicle Mixtures *(a)*
0	2.00 ± 0.08 *(b)*
1	1.90 ± 0.08
2	1.74 ± 0.08
4	1.94 ± 0.08
7	2.04 ± 0.08

(a) Corrected for a spike recovery of 59.8% ± 2.4%.
(b) Original concentration of benzyl acetate in corn oil at time of sample preparation, 2.00%, with a variation among samples of 0.05%.

D. CONCLUSION

Benzyl acetate mixed with corn oil at the 2% dose level is stable when stored at room temperature (25°C) for 7 days. If stored at 5°C, the solution should be stable for 4 weeks.

APPENDIX L
ANALYSIS OF DOSAGE MIXTURES OF BENZYL ACETATE

APPENDIX L

A. Method used until April 4, 1979:

Samples of benzyl acetate were received as corn oil mixtures. Aliquots (0.50 ml) were dissolved in 10.0 ml of chloroform. Analysis was by vapor-phase chromatography under the following conditions:

Instrument: Perkin-Elmer 910
Detection: Flame ionization
Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Temperatures: Inlet, 140°C
Oven, 100°C, isothermal
Detector, 170°C
Injection Size: 2 μl
Retention Time: 2.8 min

There was no correction for workup loss, since samples were injected without any extraction or workup procedure. The gavage samples were compared with reference standards of benzyl acetate which were prepared volume/volume in corn oil, dissolved in chloroform in the same manner as the gavage samples, and analyzed under the same chromatographic conditions.

B. Method used after April 1979:

Samples of benzyl acetate were received as corn oil mixtures in sealed syringe bottles. The samples were extracted with methanol for 3 minutes (20 ml of methanol with 0.5 ml of sample made up in corn oil). Analysis was by vapor-phase chromatography. Conditions were as follows:

Instrument: Sigma 1
Column: 3% OV-17 on 80/100 Supelcoport, 1.8 m x 4 mm I.D., glass
Detection: Flame ionization
Temperatures: Inlet, 140°C
Oven, 100°C, isothermal
Detector, 170°C
Carrier gas: Helium
Injection Size: 1 μl
Retention Time: 2.5 min

The gavage samples were compared with reference standards of benzyl acetate prepared volume/volume in corn oil, then extracted with methanol in the same manner as the sample. There was no correction applied to the samples since samples and reference standard were treated in the same manner.

C. Results

See Table L1.

TABLE L1. ANALYSIS OF BENZYL ACETATE/CORN OIL MIXTURES

Date Mixed	Week Used	Target Concentration of Benzyl Acetate in Corn Oil			
		8.325%	10.0%	16.65%	20.0%
10/16/78	10/21/78				19.0
11/13/78	11/18/78				18.8
12/11/78	12/16/78			15.6	
01/08/79	01/13/79				18.6
02/08/79	02/12/79			15.0	
03/05/79	03/10/79				21.1
04/05/79	04/09/79			15.0	
04/30/79	05/07/79				19.4 (MRI, 17.7) *(a)*
05/28/79	06/04/79			16.8	
06/25/79	06/31/79				18.7
07/23/79	07/28/79			16.6	
08/20/79	08/27/79				20.6
09/17/79	09/24/79			16.8	
10/15/79	10/22/79				20.2 (MRI, 21.3) *(a)*
11/12/79	11/19/79			17.0	
12/13/79	12/17/79				20.4
01/07/80	01/14/80			18.3	19.8
02/04/80	02/10/80	8.16	9.9		
03/03/80	03/09/80			16.8 (MRI, 16.8) *(a)*	20.1
03/31/80	04/05/80	8.93	11.0		
04/28/80	05/02/80			16.2	20.2
05/26/80	05/31/80	7.92	9.9		
06/23/80	06/30/80			16.9	20.0
07/21/80	07/28/80	8.20	10.4		
08/18/80	08/25/80			16.8 (MRI, 16.2) *(a)*	
09/15/80	09/22/80	8.22			
10/13/80	10/19/80			16.9	
11/10/80	11/17/80	7.8 (MRI, 8.2) *(a)*			
Mean (%)		8.21	10.3	16.52	19.76
Standard deviation		0.39	0.52	0.89	0.79
Coefficient of variation (%)		4.8	5.0	5.4	4.0
Range (%)		7.80-8.93	9.9-11.0	15.0-18.3	18.6-21.1

(a) Results of referee analysis at Midwest Research Institute.

APPENDIX M
POSITION OF CAGES OF F344/N RATS ON THE 2-YEAR STUDY OF BENZYL ACETATE

TABLE M1. POSITION OF CAGES AND COMBINED INCIDENCE OF RETINOPATHY OR CATARACTS IN F344/N RATS ON THE 2-YEAR STUDY OF BENZYL ACETATE

Rack A		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
High-Dose	Animal No.	1-5	6-10	11-15	16-20	21-25
Males	Incidence	2/5	4/5	5/5	5/5	3/5
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	0/5	0/5	1/5	0/5	0/5
		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
High-Dose	Animal No.	1-5	6-10	11-15	16-20	21-25
Females	Incidence	0/5	0/5	0/5	0/5	0/5
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	0/5	0/5	1/5	0/5	0/5
		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
Low-Dose	Animal No.	1-5	6-10	11-15	16-20	21-25
Males	Incidence	0/5	0/5	0/5	0/5	0/5
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	0/5	0/5	0/5	0/5	0/5
Rack B		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
Low-Dose	Animal No.	1-5	6-10	11-15	16-20	21-25
Females	Incidence	3/5	4/5	4/5	3/5	2/5
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	1/5	0/5	1/5	0/5	0/5
		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
Vehicle	Animal No.	1-5	6-10	11-15	16-20	21-25
Control	Incidence	0/5	0/5	0/5	0/5	0/5
Males						
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	0/5	0/5	1/5	0/5	0/5
		Cage 1	Cage 2	Cage 3	Cage 4	Cage 5
Vehicle	Animal No.	1-5	6-10	11-15	16-20	21-25
Control	Incidence	0/5	0/5	0/5	0/5	0/5
Females						
		Cage 6	Cage 7	Cage 8	Cage 9	Cage 10
	Animal No.	26-30	31-35	36-40	41-45	46-50
	Incidence	0/5	0/5	0/5	0/5	0/5

APPENDIX N
NTP SENTINEL ANIMAL PROGRAM

TABLE N1. FREQUENCY OF POSITIVE VIRAL DETERMINATION TABULATED BY TIME ON STUDY FOR SENTINEL RATS

		DAYS ON STUDY					
	VIRAL DETER.	0-120	121-270	271-450	451-630	>630	TOTAL
H1	NEG	0	10	10	10	10	40
	%	0%	100%	100%	100%	100%	100%
	POS	0	0	0	0	0	0
	%	0%	0%	0%	0%	0%	0%
	TOTAL	0	10	10	10	10	40
	%	0%	25%	25%	25%	25%	100%
KRV	NEG	0	10	9	9	10	38
	%	0%	100%	90%	90%	100%	95%
	POS	0	0	1	1	0	2
	%	0%	0%	10%	10%	0%	5%
	TOTAL	0	10	10	10	10	40
	%	0%	25%	25%	25%	25%	100%
PVM	NEG	0	10	10	10	10	40
	%	0%	100%	100%	100%	100%	100%
	POS	0	0	0	0	0	0
	%	0%	0%	0%	0%	0%	0%
	TOTAL	0	10	10	10	10	40
	%	0%	25%	25%	25%	25%	100%
RCV	NEG	0	6	10	10	10	36
	%	0%	100%	100%	100%	100%	100%
	POS	0	0	0	0	0	0
	%	0%	0%	0%	0%	0%	0%
	TOTAL	0	6	10	10	10	36
	%	0%	17%	28%	28%	28%	100%
SENDAI	NEG	0	0	0	0	1	1
	%	0%	0%	0%	0%	10%	2%
	POS	0	10	10	10	9	39
	%	0%	100%	100%	100%	90%	97%
	TOTAL	0	10	10	10	10	40
	%	0%	25%	25%	25%	25%	100%

TABLE N2. FREQUENCY OF POSITIVE VIRAL DETERMINATION TABULATED BY TIME ON STUDY FOR SENTINEL MICE

		DAYS ON STUDY					
	VIRAL DETER.	0-120	121-270	271-450	451-630	>630	TOTAL
MHV	NEG	0	0	6	2	9	17
	%	0%	0%	100%	22%	100%	71%
	POS	0	0	0	7	0	7
	%	0%	0%	0%	78%	0%	29%
	TOTAL	0	0	6	9	9	24
	%	0%	0%	25%	38%	38%	100%
MVM	NEG	0	9	6	9	10	34
	%	0%	100%	100%	100%	100%	100%
	POS	0	0	0	0	0	0
	%	0%	0%	0%	0%	0%	0%
	TOTAL	0	9	6	9	10	34
	%	0%	26%	18%	26%	29%	100%
PVM	NEG	0	4	4	9	8	25
	%	0%	44%	67%	100%	80%	74%
	POS	0	5	2	0	2	9
	%	0%	56%	33%	0%	20%	26%
	TOTAL	0	9	6	9	10	34
	%	0%	26%	18%	26%	29%	100%
RE03	NEG	0	9	6	8	10	33
	%	0%	100%	100%	89%	100%	97%
	POS	0	0	0	1	0	1
	%	0%	0%	0%	11%	0%	3%
	TOTAL	0	9	6	9	10	34
	%	0%	26%	18%	26%	29%	100%
SENDAI	NEG	0	0	0	1	5	6
	%	0%	0%	0%	11%	56%	18%
	POS	0	9	6	8	4	27
	%	0%	100%	100%	89%	44%	82%
	TOTAL	0	9	6	9	9	33
	%	0%	27%	18%	27%	27%	100%

APPENDIX O

DATA AUDIT SUMMARY

DATA AUDIT SUMMARY

The experimental data and the draft Technical Report on the toxicology and carcinogenesis studies of benzyl acetate were examined for completeness, accuracy, and compliance with Good Laboratory Practice procedures during September 19-21, 1983. The following persons were involved in the audit: National Toxicology Program, Dr. K.M. Abdo, Chemical Manager, Toxicologist; Ms. C. Davies, Chemist; Dr. B. Schwetz, Toxicologist and Audit Team Leader; Dr. C. Whitmire, Quality Assurance; and Dr. M. Wolfe, Pathologist; Experimental Pathology Laboratory, Inc. (EPL), Dr. D.A. Banas, Pathologist; Tracor Jitco, Dr. P. Hildebrandt, Pathologist; Clement Associates, Dr. M. Anver, Pathologist.

The full audit report is on file at the National Toxicology Program, NIEHS. The main findings are related to pathology. The findings and their resolutions are as follows:

The mouse liver, which was considered to be a target organ for evaluation in the draft Technical Report, had not been reviewed by the Quality Assurance or the Pathology Working Group. Thus all the livers were reviewed. The following observations were noted: one additional adenoma was found in a high dose male; five animals with gross lesions in the liver and one animal with a gross lesion in the kidney were not cut in; and slides of livers for one high dose female and one low dose male appeared to be shattered in the area of histologic change, which made diagnosis difficult.

A number of corrections were required for the diagnoses of mouse stomach (including forestomach) lesions. The corrected diagnoses are reflected in the tables in the final Technical Report.

All pancreata remaining in the wet tissues of several male rat studies with corn oil vehicle controls were examined, including those of the benzyl acetate study, to determine the effects of size of sampling area on the incidence of pancreatic lesions. All pancreata from treated rats were embedded and sectioned in the same manner as were the controls. The data were evaluated and tabulated, after which all pancreatic slides were sent to the original pathologist for review.

All the above findings and recommendations were communicated to the original pathologist and incorporated in the final tables. The data and conclusions presented in this final Technical Report reflect those resolutions.

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