NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF BENZOPHENONE

(CAS NO. 119-61-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

February 2006

NTP TR 533

NIH Publication No. 06-4469

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

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CONTENTS

SUMMARY

Background

Benzophenone is an ingredient in a variety of chemical products including plastics, adhesives, insecticides, and pharmaceuticals. It is also used in fragrances and as a flavoring in foods. We studied the effects of benzophenone on male and female rats and mice to identify potential toxic or carcinogenic hazards to humans.

Methods

We gave feed containing benzophenone to groups of 50 animals for 2 years. Male and female rats and mice received 312, 625, or 1,250 parts per million of benzophenone in their feed (the highest concentration corresponding to 0.125%). Groups of animals receiving untreated feed served as controls. Tissues from more than 40 sites were examined for every animal.

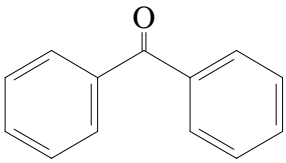
Results

Almost all of the male rats receiving the highest concentration died before the end of the study. Male and female rats and female mice receiving benzophenone weighed less than the controls. Male rats receiving benzophenone had more severe kidney nephropathy than control animals and higher incidences of kidney tumors and leukemia. Female rats receiving benzophenone also had slightly higher rates of leukemia. Male and female mice had slightly increased rates of liver tumors and also increased severities of kidney nephropathy, metaplasia of the epithelium of the nose, and hyperplasia of the spleen. Some female mice also developed rare histiocytic sarcomas.

Conclusions

We conclude that benzophenone caused kidney cancer in male rats, liver tumors in male mice, and histiocytic sarcomas in female mice. Benzophenone may also have been associated with development of leukemia in male and female rats and with liver tumors in female mice.

ABSTRACT



BENZOPHENONE

CAS No. 119-61-9

Chemical Formula: $C_{13}H_{10}O$ Molecular Weight: 182.22

Synonyms: Benzene, benzophenone (8CI); benzoyl; benzoylbenzene; benzoylbenzenephenyl; diphenyl ketone; diphenylmethanone; methanone, diphenyl-(9CI); α-oxodiphenylmethane; α-oxoditane; phenyl ketone

Benzophenone is used as a photoinitiator, a fragrance enhancer, an ultraviolet curing agent, and occasionally as a flavor ingredient; it is also used in the manufacture of insecticides, agricultural chemicals, and hypnotics, antihistamines, and other pharmaceuticals; and it is used as an additive in plastics, coatings, and adhesive formulations. Benzophenone was nominated for study by the National Institute of Environmental Health Sciences based on its potential for occupational and consumer exposure and the lack of long-term toxicity data. Male and female F344/N rats and B6C3F$_1$ mice were exposed to benzophenone (greater than 99% pure) in feed for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium,* mouse bone marrow cells, and mouse peripheral blood erythrocytes. Results of 14-week toxicity studies in F344/N rats and B6C3F$_1$ mice were reported earlier (NTP, 2000).

2-Year Study in Rats

Groups of 50 male and 50 female rats were fed diets containing 0, 312, 625, or 1,250 ppm benzophenone (equivalent to average daily doses of approximately 15, 30, and 60 mg benzophenone/kg body weight to males and 15, 30, and 65 mg/kg to females) for 105 weeks. Survival of 1,250 ppm males was significantly less than that of controls. Mean body weights of 1,250 ppm males were markedly less than those of the controls during year 2 of the study, and weights of exposed females were consistently less than controls throughout the study. Feed consumption by 1,250 ppm males was less than that by the controls after week 70; feed consumption by 1,250 ppm females was generally less than that by the controls throughout the study.

There was a positive trend in the incidences of renal tubule adenoma in males, and the incidences in 625 and 1,250 ppm males exceeded the historical control range for all routes; these neoplasms were accompanied by significantly increased incidences of renal tubule hyperplasia. Due to these findings, additional kidney sections were evaluated; results indicated additional renal tubule adenomas in all groups of males and renal tubule hyperplasia in all groups of males and females. The incidences of pelvic transitional epithelium hyperplasia and the severity of nephropathy were significantly increased in all exposed groups of male rats.

Increased incidences of mononuclear cell leukemia in all exposed groups of females exceeded the historical

control range from feed studies, and the incidence in 625 ppm females was significantly greater than that in the controls. Male rats exposed to 312 or 625 ppm had significantly increased incidences of mononuclear cell leukemia. One 625 ppm female and two 1,250 ppm females had histiocytic sarcomas, and the incidence in the 1,250 ppm group exceeded the range in the historical controls.

Liver lesions included significantly increased incidences of hepatocytic centrilobular hypertrophy in all exposed groups of males and females, cystic degeneration in 625 and 1,250 ppm males, and bile duct hyperplasia in all exposed groups of females.

Incidences of mammary gland fibroadenoma in females exposed to 625 or 1,250 ppm were lower than expected after adjusting for body weight.

2-Year Study in Mice

Groups of 50 male and 50 female mice were fed diets containing 0, 312, 625, or 1,250 ppm benzophenone (equivalent to average daily doses of approximately 40, 80, and 160 mg/kg body weight to males and 35, 70, and 150 mg/kg to females) for 105 weeks. Survival of all exposed groups of mice was generally similar to that of the control groups. Mean body weights of exposed females were less than vehicle controls. Feed consumption by exposed males and females was similar to that by the controls.

In male mice, there were significantly increased incidences of hepatocellular adenoma in the 625 and 1,250 ppm groups, and these incidences exceeded the historical control range. All hepatocellular neoplasms combined occurred with a positive trend. In female mice, the incidences of hepatocellular adenoma in the 625 and 1,250 ppm groups were higher than expected after adjusting for the lower body weights in these groups. Incidences of centrilobular hepatocyte hypertrophy were significantly increased in all exposed groups of males and females. All exposed groups of male mice had significant increases in the incidences of multinucleated hepatocytes and chronic active inflammation. The incidences of cystic degeneration of hepatocytes in 625 and 1,250 ppm males were significantly increased. The incidence of histiocytic sarcoma in 625 ppm females was significantly increased and exceeded the historical control range.

The incidences of kidney nephropathy and mineralization in exposed groups of females and the severity of nephropathy in exposed groups of males were significantly increased.

The incidences of metaplasia of the olfactory epithelium were significantly increased in 1,250 ppm males and females. The incidences of hyperplasia of lymphoid follicles in the spleen were significantly increased in all exposed groups of males and in 312 and 625 ppm females.

Genetic Toxicology

Benzophenone was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without hamster or rat liver activation enzymes. No significant increases in the frequencies of micronucleated polychromatic erythrocytes were seen in bone marrow samples from male mice administered benzophenone three times by intraperitoneal injection. In addition, no increases in micronucleated normochromatic erythrocytes were noted in peripheral blood of male or female mice administered benzophenone for 14 weeks in dosed feed.

Conclusions

Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity** of benzophenone in male F344/N rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344/N rats may have been related to benzophenone exposure. There was *equivocal evidence of carcinogenic activity* of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma. There was *some evidence of carcinogenic activity* of benzophenone in male B6C3F_1 mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was *some evidence of carcinogenic activity* of benzophenone in female B6C3F_1 mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female B6C3F_1 mice may have been related to benzophenone exposure.

Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats

and in the liver, kidney, nose, and spleen of male and female mice.

Decreased incidences of mammary gland fibroadenoma in female rats were related to benzophenone exposure.

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

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in feed	0, 312, 625, 1,250 ppm	0, 312, 625, 1,250 ppm	0, 312, 625, 1,250 ppm	0, 312, 625, 1,250 ppm
Body weights	625 and 1,250 ppm groups less than the control group	625 and 1,250 ppm groups less than the control group	Exposed groups similar to the control group	312, 625, and 1,250 ppm groups less than the control group
Survival rates	22/50, 27/50, 31/50, 2/50	32/50, 38/50, 37/50, 34/50	44/50, 44/50, 44/50, 45/50	40/50, 42/50, 41/50, 31/50
Nonneoplastic effects	Kidney: renal tubule, hyperplasia (standard evaluation - 1/50, 5/50, 20/50, 23/50; standard and extended evaluations combined - 3/50, 11/50, 30/50, 40/50); pelvis, transitional epithelium, hyperplasia (1/50, 11/50, 29/50, 34/50); severity of nephropathy (1.3, 2.4, 3.3, 3.8) Liver: hepatocyte, centrilobular, hypertrophy (0/50, 17/50, 31/50, 19/50); degeneration, cystic (8/50, 11/50, 20/50, 15/50)	Kidney: renal tubule, hyperplasia (standard evaluation - 0/50, 1/50, 1/50, 1/50; standard and extended evaluations combined - 1/50, 8/50, 10/50, 7/50); severity of nephropathy - (1.1, 1.4, 1.7, 2.0) Liver: hepatocyte, centrilobular, hypertrophy (0/50, 27/50, 30/50, 33/50); bile duct, hyperplasia (10/50, 35/50, 39/50, 40/50)	Liver: hepatocyte, centrilobular, hypertrophy (0/50, 44/50, 50/50, 48/50); hepatocyte, multinucleated (0/50, 41/50, 47/50, 48/50); inflammation, chronic active (33/50, 47/50, 44/50, 42/50); hepatocyte, degeneration, cystic (0/50, 0/50, 5/50, 30/50) Kidney: severity of nephropathy (1.2, 1.4, 1.7, 3.0) Nose: olfactory epithelium, metaplasia (0/50, 2/50, 2/50, 24/50) Spleen: lymphoid follicle, hyperplasia, lymphoid (17/50, 31/50, 34/50, 32/50)	Liver: hepatocyte, centrilobular, hypertrophy (0/50, 29/50, 44/50, 37/50) Kidney: nephropathy (21/50, 33/50, 31/50, 30/50); mineralization (15/50, 31/50, 36/50, 49/50); severity of nephropathy - (1.2, 1.1, 1.5, 1.7) Nose: olfactory epithelium, metaplasia (0/50, 0/50, 0/50, 39/50) Spleen: lymphoid follicle, hyperplasia, lymphoid (24/50, 36/50, 37/50, 22/50)
Neoplastic effects	Kidney: renal tubule, adenoma (standard evaluation - 1/50, 1/50, 2/50, 4/50; standard and extended evaluations combined - 2/50, 2/50, 7/50, 8/50)	None	Liver: hepatocellular adenoma (11/50, 15/50, 23/50, 23/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (18/50, 20/50, 25/50, 29/50)	Histiocytic sarcoma: (0/50, 0/50, 5/50, 3/50)
Equivocal findings	Mononuclear cell leukemia: (27/50, 41/50, 39/50, 24/50)	Mononuclear cell leukemia: (19/50, 25/50, 30/50, 29/50) Histiocytic sarcoma: (0/50, 0/50, 1/50, 2/50)	None	Liver: hepatocellular adenoma (5/50, 4/50, 10/50, 8/50)

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Decreased incidences	None	Mammary gland: fibroadenoma (27/50, 24/50, 15/50, 7/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	Some evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9		
Micronucleated erythrocytes				
Mouse bone marrow *in vivo:*		Negative		
Mouse peripheral blood *in vivo:*		Negative		

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on benzophenone on December 9, 2004, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On December 9, 2004, the draft Technical Report on the toxicology and carcinogenesis studies of benzophenone received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of benzophenone by describing the uses of the chemical and the rationale for the study, the design and dose selection for the feed studies, the survival and body weight effects, and the compound-related neoplasms and nonneoplastic lesions in rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *some evidence of carcinogenic activity* in male and female B6C3F$_1$ mice. The incidences of mononuclear cell leukemia in male rats and of hepatocellular adenoma in female mice may have been related to benzophenone exposure.

Dr. Storer, the first principal reviewer, commented that the study was well conducted. He asked for more discussion on the interpretation of the conflicting genetic toxicology data and if there was a link between the histiocytic sarcoma and the mononuclear cell leukemia.

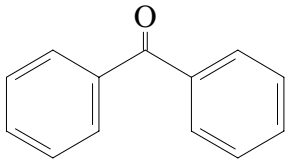
Dr. Roberts, the second principal reviewer, agreed with the conclusions and noted that the dose formulations were often less than the target concentrations and were sometimes contaminated.

Dr. Elwell, the third principal reviewer, questioned the explanations for some of the choices of equivocal evidence versus some evidence, particularly for mononuclear cell leukemia in rats and histiocytic sarcoma in female rats.

Dr. J.R. Hailey, NIEHS, replied that there have been many studies in rats where there was an increased incidence of mononuclear cell leukemia with no increased incidence of histiocytic sarcoma. He also added that the mononuclear cell leukemias were considered an equivocal response because the incidences in the control and exposed groups were all unusually high but with no difference in severity. Dr. Hailey noted that the overall incidence of histiocytic sarcoma consisted of only three neoplasms among the four exposed groups, and it was possible that the distribution was spurious.

Dr. Storer moved that the conclusions be accepted as written. Dr. Roberts seconded the motion, which was approved unanimously with nine votes.

INTRODUCTION



BENZOPHENONE

CAS No. 119-61-9

Chemical Formula: $C_{13}H_{10}O$ Molecular Weight: 182.22

Synonyms: Benzene, benzophenone (8CI); benzoyl; benzoylbenzene; benzoylbenzenephenyl; diphenyl ketone; diphenylmethanone; methanone, diphenyl-(9CI); α-oxodiphenylmethane; α-oxoditane; phenyl ketone

Chemical and Physical Properties

Benzophenone, an aryl ketone, is a colorless crystalline solid with a geranium- or rose-like odor. There are two forms of benzophenone, α and β. These studies were conducted using the α, orthorhombic, stable form of the compound. Benzophenone has melting points of 49° C (α) and 26° C (β), a boiling point of 305.4° C, a flash point greater than 110° C, a vapor pressure of 1 mm Hg at 108.2° C, specific gravities of 1.0976 at 50° C/50° C (α) and 1.108 at 23° C/40° C (β), a refractive index of 1.60, and a log octanol:water partition coefficient of 3.18. It is insoluble in water and soluble in organic solvents such as alcohol, acetone, ether, acetic acid, chloroform, and benzene (Hansch and Leo, 1979; *Merck Index*, 1996; Lewis, 1997). Benzophenone is photochemically reactive, incompatible with strong oxidizing and reducing agents, and may attack some plastics. Decomposition of benzophenone produces toxic fumes of carbon monoxide and carbon dioxide (*Sigma-Aldrich*, 1988).

Production, Use, and Human Exposure

Benzophenone is prepared in 66% yield by a Friedel-Crafts acylation using benzoyl chloride with an excess of benzene in the presence of anhydrous aluminum chloride (Furia and Bellanca, 1975; *Kirk-Othmer*, 1978). It is classified as a high volume chemical, with production exceeding 1 million pounds per year in the United States (USEPA, 2003).

Benzophenone is used primarily as a photoinitiator and fragrance enhancer (Anonymous, 1990; CBNB, 1991), and it is also used in the manufacture of insecticides, agricultural chemicals, and hypnotics, antihistamines, and other pharmaceuticals; as an ultraviolet curing agent in sunglasses and ink; as an additive in plastics, coatings, and adhesive formulations; and, occasionally, as a flavor ingredient. Concentrations of benzophenone in food products range from 0.57 ppm in nonalcoholic beverages to 3.27 ppm in frozen dairy products; it may also be an ingredient in baked goods, soft candy, gelatins, and puddings (NAS/NRC, 1979).

Because of its high octanol:water partition coefficient and its insolubility in water, benzophenone will partition in soil and sediment (USEPA, 1984); the adsorption of benzophenone to soil is proportional to the organic content of the soil (OHMTADS, 1991). Although benzophenone has been identified in the atmosphere, it is difficult to determine whether its presence is due to its being a direct product of combustion or a secondary

product of atmospheric degradation (Helmig *et al*., 1989). Leary *et al.* (1987) found that benzophenone is a component of emissions from a standard residential oil burner. It has also been detected in surface and groundwater samples, primarily from the discharge of raw sewage and wastewater into waterways. Based on the use of benzophenone as an additive in fragrances, cosmetics, toiletries, pharmaceuticals, insecticides, and flavor ingredients, consumer exposure may be significant. Additionally, surveys showed that 41,520 workers in the United States were potentially exposed to benzophenone between 1981 and 1983 (NIOSH, 1990).

Absorption, Distribution, Metabolism, and Excretion

In rhesus monkeys, percutaneous absorption of benzophenone was found to be 44% and 69% for unoccluded and occluded sites, respectively (Bronaugh *et al.*, 1990). The primary pathway of benzophenone metabolism following dietary administration in rabbits was reported to be reduction of the keto group to yield benzhydrol, which was excreted at concentrations of 41% to 61% of the administered dose as a labile glucuronide in the urine (Robinson and Williams, 1957; Robinson, 1958). In male Sprague-Dawley rats that received benzophenone by gavage, 1% of the administered dose was detected as *p*-hydroxybenzophenone in enzyme-treated urine samples but not in unhydrolyzed urine (Stocklinski *et al.*, 1980). No *p*-hydroxybenzophenone was detected in the feces.

The metabolism of benzophenone was investigated in isolated rat hepatocytes at a low toxic level of 0.25 mM. Benzophenone was enzymatically converted to at least three metabolites: benzhydrol, *p*-hydroxybenzophenone, and a sulfate (Nakagawa *et al.*, 2000) (Figure 1). Benzhydrol is produced by a reduction of the carbonyl group to the corresponding secondary alcohol. Benzophenone is converted to *p*-hydroxybenzophenone probably by a cytochrome P450 enzyme. The amount of free *p*-hydroxybenzophenone was less than that of the sulfate, which accumulated in hepatocyte suspensions with time. In a subsequent study (Nakagawa and Tayama, 2002), 6 hours after a single oral dose of 100 or 400 mg benzophenone/kg body weight, female Sprague-Dawley rats (four per group) displayed serum concentrations of benzhydrol > benzophenone > *p*-hydroxybenzophenone.

Toxicity

Experimental Animals

Median lethal (LD_{50}) doses of benzophenone given by oral, intraperitoneal, and dermal routes of administration are given in Table 1; these data indicate that benzophenone is only slightly toxic.

In 14-week studies, benzophenone was administered to groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice in feed at concentrations of 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm (NTP, 2000). The estimated daily dose ranged from 75 to 850 mg benzophenone/kg body weight for male rats; 80 to 1,000 mg/kg for female rats; 200 to 3,300 mg/kg for male mice; and from 270 to 4,200 mg/kg for female mice. Benzophenone was unpalatable for both rats and mice at 20,000 ppm. All 20,000 ppm rats had significant body weight loss and were terminated on days 39 or 40; all other rats survived to the end of the study. All male mice and four female mice in the 20,000 ppm groups died or were sacrificed moribund prior to the end of the study. There was no exposure-related mortality in the remaining groups. Significantly decreased body weights relative to the controls occurred in all exposed groups of female rats and in all exposed groups of male rats, except the 1,250 ppm group. Lower body weights were apparent in 10,000 ppm male male mice and in 5,000 ppm or greater female mice.

In the 14-week study in rats, benzophenone toxicity occurred in the liver, kidney, and hematopoietic system of males and females (Table 2; NTP, 2000); exposure-related increases in liver weights were attributed to centrilobular hypertrophy and cytoplasmic vacuolization of hepatocytes. Exposure-related increases in alanine aminotransferase and bile salt concentrations indicated a hepatic effect consistent with the gross and microscopic liver changes. These alterations were accompanied by benzophenone-induced increases in pentoxyresorufin dealkylase, an enzyme activity linked to the cytochrome P450 2B isomer. Exposure-related increases in kidney weights were associated with renal changes in exposed male and female rats. These lesions included tubule dilatation, protein casts, tubule epithelial regeneration, mineralization, and necrosis in renal papillae. Unique lesions were well-demarcated, wedge-shaped areas of prominent tubule dilatation. Renal tubule dilatation occurred in 2,500 ppm or greater males and in 10,000 and 20,000 ppm females. Incidences and/or severities of focal tubule regeneration were increased relative to the

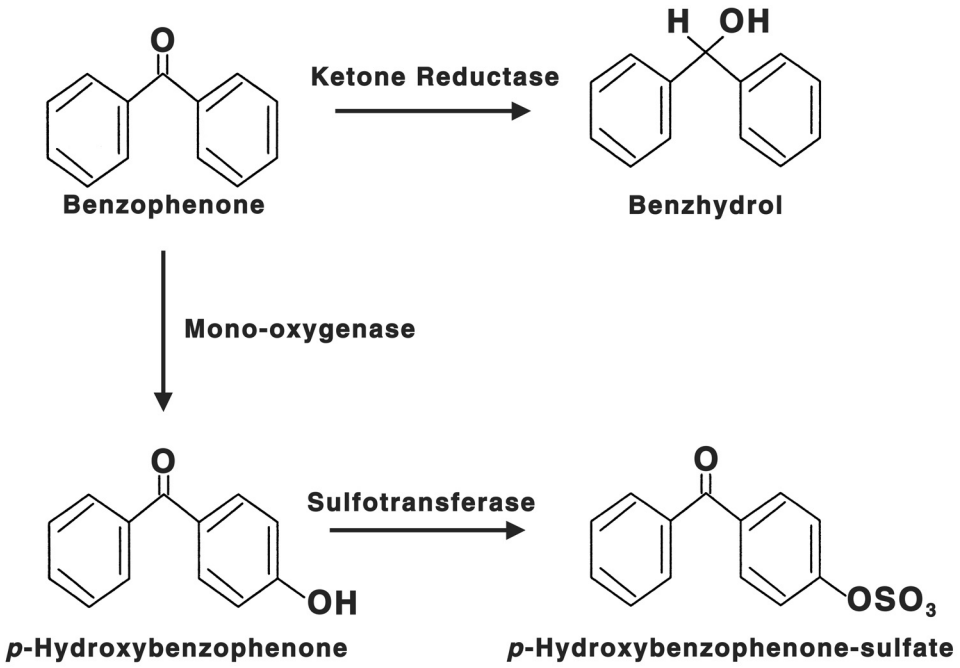


FIGURE 1
Proposed Metabolism of Benzophenone
(adopted from Nakagawa *et al.*, 2000)

TABLE 1
Summary of Selected Acute Animal Toxicity Data for Benzophenone

Species	Route of Administration	LD_{50} (mg/kg)	Reference
Rat	Oral	>10,000	Opdyke, 1973
Rat	Oral	1,900	Eastman Kodak Company, 1991
Mouse	Oral	2,895 (2,441-3,434)	Caprino *et al*., 1976
Mouse	Intraperitoneal	727 (634-833)	Caprino *et al*., 1976
Rabbit	Dermal	3,535 (2,007-6,226)	Opdyke, 1973

TABLE 2
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Week Feed Study of Benzophenone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Liver[b]	10	10	10	10	10	10
Hepatocyte, Hypertrophy[c]	0	0	0	0	5* (1.2)[d]	7** (1.0)
Hepatocyte, Vacuolization Cytoplasmic	1 (1.0)	10** (1.0)	10** (1.0)	10** (1.0)	10** (1.4)	10** (1.2)
Kidney	10	10	10	10	10	10
Renal Tubule, Dilatation	0	0	6** (1.0)	8** (1.0)	9** (1.3)	8** (1.8)
Renal Tubule, Protein Casts	0	8** (1.0)	8** (1.0)	9** (1.2)	10** (1.3)	0
Renal Tubule, Regeneration	10 (1.0)	10 (2.0)	10 (1.5)	10 (2.0)	10 (2.0)	8 (1.6)
Mineralization	0	0	0	5* (1.0)	10** (1.1)	0
Papilla, Necrosis	0	0	0	0	2 (1.0)	6** (1.2)
Female						
Liver	10	10	10	10	10	9
Hepatocyte, Hypertrophy	0	2 (1.0)	8** (1.0)	10** (1.1)	10** (1.0)	7** (1.0)
Hepatocyte, Vacuolization Cytoplasmic	0	0	0	9** (1.1)	10** (1.0)	7** (1.1)
Kidney	10	10	10	10	10	9
Renal Tubule, Dilatation	0	0	0	0	3 (1.0)	5* (1.6)
Renal Tubule, Protein Casts	0	0	2 (1.0)	0	4* (1.0)	0
Renal Tubule, Regeneration	3 (1.0)	8* (1.0)	6 (1.0)	6 (1.0)	9** (1.2)	7 (1.6)
Mineralization	10 (1.5)	10 (1.6)	10 (1.6)	10 (1.1)	10 (1.2)	9 (1.2)
Papilla, Necrosis	0	0	0	0	0	3 (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] NTP, 2000
[b] Number of animals with tissue examined microscopically
[c] Number of animals with lesion
[d] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, and 4=marked

controls in exposed males and females. Secondary lesions due to inanition resulted in atrophy of bone marrow in both sexes and testicular hypoplasia in males. Hematology results indicated mild anemia, altered circulating erythroid mass, and transient exposure concentration-related increases in platelet counts. At necropsy, three males had small seminal vesicles; microscopic examination revealed that these were immature seminal vesicles.

Mice exposed to benzophenone in the 14-week study were less sensitive to the effects of exposure compared to rats, requiring higher doses on a body weight basis to display benzophenone toxicity (NTP, 2000). Thinness and lethargy in the high dose groups were the only clinical signs reported. There were no gross lesions observed at necropsy related to exposure to benzophenone. The liver weights were increased up to 100% in males and 62% in females. Significant microscopic findings for both sexes were limited to the liver (Table 3). Significantly increased incidences of centrilobular hypertrophy of hepatocytes that corresponded to increased liver weight were observed in the liver of all exposed groups. The severity of hepatocyte hypertrophy increased in an exposure concentration-related manner, with moderate to marked severity in all 20,000 ppm mice. Male mice exhibited evidence of anemia in the 5,000 and 10,000 ppm groups, demonstrated by minimal decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts. Liver contents of cytochrome P450 of male mice in all exposed groups, except the 10,000 ppm group, were significantly greater

TABLE 3
Incidences of Nonneoplastic Lesions of the Liver in Mice in the 14-Week Feed Study of Benzophenone[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
Number Examined Microscopically	10	10	10	10	10	10
Centrilobular, Hypertrophy[b]	3 (1.0)[c]	8* (1.0)	10** (2.0)	10** (3.0)	10** (3.0)	10** (3.2)
Hepatocyte, Vacuolization Cytoplasmic	0	0	0	0	0	3 (2.0)
Inflammation, Chronic Active	5 (1.0)	4 (1.0)	8 (1.0)	8 (1.0)	5 (1.0)	1 (1.0)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Centrilobular, Hypertrophy	3 (1.0)	9** (1.0)	10** (2.0)	10** (3.0)	10** (3.0)	10** (4.0)
Hepatocyte, Vacuolization Cytoplasmic	0	0	0	2 (1.0)	9** (2.4)	1 (1.0)
Inflammation, Chronic Active	8 (1.0)	9 (1.1)	9 (1.0)	9 (1.0)	9 (1.0)	3 (1.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] NTP, 2000
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, and 4=marked

than in the vehicle controls. The testis and epididymis weights of male mice in the 10,000 ppm group were significantly less than those of controls, but sperm motility parameters were normal. As in rats, kidney weights were increased in all exposed animals, except in the 1,250 ppm group. However, unlike in rats, there were no microscopic effects to account for the increased weights.

Benzophenone induced histological alterations in the liver of guinea pigs (Dutta *et al*., 1993). An unspecified number of male guinea pigs received intraperitoneal injections of 5 mg benzophenone/kg body weight daily for 15 days. Microscopic evaluation of the liver revealed disorganization of lobular architecture and hepatic cords, nuclear hyperchromatia, and hepatocellular necrosis.

Groups of male rats (strain not specified) were fed diets containing 0.1% or 1.0% benzophenone for 10 consecutive days (USEPA, 1984). Feed consumption and body weights were slightly reduced in the 1.0% group. Exposure concentration-dependent increases in absolute and relative liver weights and relative kidney weight were observed. Serum alanine aminotransferase activity of rats in the 1.0% group was increased compared to that of the controls. Mild degenerative effects were observed in the liver and bone marrow of rats in the 1.0% group, suggesting that the liver may be the primary target of the toxic effects of benzophenone and that the bone marrow may also be a target.

Benzophenone was administered in feed to Sprague-Dawley rats at concentrations of 20 mg/kg body weight per day for 90 days or 100 or 500 mg/kg per day for 28 days (Burdock *et al.*, 1991). Decreases in hematocrit values, erythrocyte counts, and hemoglobin concentrations were observed in 100 and 500 mg/kg females; a decrease in hemoglobin concentration was also evident in 500 mg/kg males. Males in the 100 and 500 mg/kg groups had increased urea nitrogen concentrations; total bilirubin and protein were increased in 500 mg/kg males and in 100 and 500 mg/kg females. Males and females exposed to 100 or 500 mg/kg had increased albumin concentrations and absolute and relative liver and kidney weights. Histopathologic examination of the liver revealed hepatocellular enlargement with associated clumping of cytoplasmic basophilic material around the central vein in rats in the 100 and 500 mg/kg groups.

Slight skin irritation, evidenced by slight erythema and desquamation and slight to moderate edema, was observed in guinea pigs that received dermal applications of benzophenone on the abdomen for 24 hours under an occlusive wrap or uncovered on the back for 10 days (USEPA, 1984). Additional exposures to benzophenone failed to exacerbate the irritation. In a dermal study using the Draize method, benzophenone was determined to have medium irritation potential, with a primary cutaneous irritation index of 2.0 in rabbits (Calas *et al.*, 1977). Additional experiments were conducted by these investigators in guinea pigs to determine skin irritation and contact hypersensitivity induced by benzophenone; in the open epicutaneous test, the Draize test, the maximization test, and a test with Freund's complete adjuvant, benzophenone did not induce allergenicity in guinea pigs.

Humans

Benzophenone in sunscreen produced an allergic skin reaction in one patient, as assessed by photopatch testing (Cook and Freeman, 2001). This compound was positive in patch test results in 1% to 2% of patients tested by the North American Contact Dermatitis Research Group (Mitchell *et al.*, 1982). Derivatives of benzophenone, particularly 2-hydroxy-4-methoxybenzophenone (benzophenone-3) and 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid (benzophenone-4), are skin irritants that cause photoallergy and have been associated with allergic contact dermatitis (Alanko *et al*., 2001) and facial erythema (Nedorost, 2003). No epidemiology studies related to benzophenone exposure in humans were found in the literature (HSDB, 2004).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

In an NTP developmental toxicity study, benzophenone was administered by gavage to timed pregnant Sprague-Dawley (CD®) rats (22 to 25 per group) at doses of 100, 200, or 300 mg/kg per day on days 6 to 19 of gestation (NTP, 2002). While there were no treatment-related maternal deaths, maternal toxicity occurred in all dosed groups. Clinical signs observed at all doses of benzophenone included lethargy, piloerection, weight loss, and rooting in bedding after dosing. Maternal liver and kidney weights were significantly increased in all dosed groups. Reduced maternal body weight gain and decreased feed consumption were observed in the 300 mg/kg group. Benzophenone had no adverse effects on prenatal viability or overall incidences of fetal malformations or variations. However, average fetal body weight per litter in the 300 mg/kg group was significantly lower than that in the vehicle controls. The incidences of unossified sternebrae were increased at all doses of benzophenone, and the incidences of extra rib on Lumbar I were increased in the 200 and 300 mg/kg groups. Although a no-observed-adverse-effect-level (NOAEL) was not achieved for developmental toxicity, the effects described above are limited to mild developmental delays with a high probability of recovery during early postnatal development.

In another NTP (2004a) study, New Zealand White rabbits (24 per group) were administered benzophenone by oral gavage at 5, 25, or 45 mg/kg on gestational days 6 to 29. Maternal body weight and feed consumption showed decreasing trends. There were no changes in the weights of the gravid uterus, liver, or kidney of treated does. Benzophenone had no significant adverse effect on prenatal viability in litters that were carried until scheduled termination on gestational day 30. Nevertheless, the ability of does to successfully carry their pregnancies was clearly compromised in a dose-related manner (0 mg/kg, 24/24; 5 mg/kg, 24/24; 25 mg/kg, 19/22; 45 mg/kg, 12/19). Fetal body weight was significantly decreased in the 45 mg/kg group only. Similar to the rat studies, developmental toxicity was noted only in the presence of well-defined maternal toxicity. Thus, there was no evidence for selective susceptibility of the conceptus relative to the pregnant dam in either the rat or the rabbit.

Immature, 21-day-old female Sprague-Dawley rats (unspecified number of animals per group) were used to compare uterotrophic effects of 17 β-estradiol, benzophenone, and two metabolites of benzophenone, *p*-hydroxybenzophenone and benzhydrol (Nakagawa and Tayama, 2001). Animals were dosed with 100, 200, or 400 mg benzophenone, *p*-hydroxybenzophenone, or benzhydrol per kg body weight via subcutaneous injection once per day for 3 days and sacrificed 6 hours after the last dose. Neither benzophenone nor benzhydrol affected uterine weight or morphology of the uterus or vagina. *p*-Hydroxybenzophenone elicited increases in absolute and relative uterine weights in a dose-dependent manner and increased the luminal epithelium height and thickness of the stromal layer of the uterus at 400 mg/kg. In the vagina, *p*-hydroxybenzophenone

increased the thickness of the epithelial cell layer, accompanied by cornification.

A subsequent study examined the effects of benzophenone on ovariectomized rats (Nakagawa and Tayama, 2002). Female Sprague-Dawley rats (five per group) were ovariectomized at 4 weeks of age, acclimated for 3 weeks, orally administered 100 or 400 mg benzophenone per kg body weight for 3 days, and sacrificed 24 hours after the last dose. The 400 mg/kg dose of benzophenone elicited approximately 1.9-fold increases in absolute and relative uterine weights. The uterine response was accompanied by increased luminal epithelium height and thickness of the stromal layer of the uterus. Additionally, benzophenone (400 mg/kg) increased the thickness of the vaginal epithelial cell layers with cornification.

The developmental and teratogenic effects of benzophenone were also studied in Japanese newts. Seven days after amputation of the forelimb at a position proximal to the elbow, benzophenone (~5 µg) was inserted in the anterior part of the regeneration blastema. No retardation of regeneration was observed, and growth continued normally in the dosed group (Tsonis and Eguchi, 1982).

Humans

No studies of reproductive or developmental effects of benzophenone in humans were found in a review of the literature.

CARCINOGENICITY

Experimental Animals

The carcinogenicity of benzophenone has been studied in female Swiss mice (Stenbäck and Shubik, 1974) and New Zealand White rabbits (Stenbäck, 1977). In lifetime studies, animals received twice-weekly topical administrations of 0.02 mL of 5%, 25%, or 50% benzophenone in acetone. Benzophenone was applied to a 1-inch square area on the dorsal skin between the flanks of mice; for rabbits, the dose was applied to the inside of the left ear. All mice died by week 110. The incidences of skin neoplasms in dosed mice were similar to those in the controls (Stenbäck and Shubik, 1974). Benzophenone had no effect on survival rates or on the incidences of neoplasms or nonneoplastic lesions in rabbits after 160 weeks of treatment (Stenbäck, 1977).

Humans

No epidemiology studies or case reports examining the relationship between exposure to benzophenone and human cancer were found in the literature.

GENETIC TOXICITY

Benzophenone was not mutagenic in the standard Ames test using various strains of *Salmonella typhimurium* (Mortelmans *et al*., 1986) or in the *Escherichia coli* Pol A assay (Fluck *et al.*, 1976). In addition, negative results were reported with benzophenone in the mouse lymphoma L5178Y/tk$^{+/-}$ cell test for induction of trifluorothymidine resistance (CCRIS, 1991). All three of these *in vitro* assays were performed with and without rodent liver S9 metabolic activation enzymes. Results of a recent investigation of the genotoxic potential of benzophenone showed no induction of DNA damage as measured by *umu* gene expression in *S. typhimurium* strain TA1535/pSK1002 in the absence or the presence of microsomes from rat, mouse, or human liver (Takemoto *et al*., 2002). However, when various human P450 preparations, including human P450 2A6 and P450 family I enzymes, were tested for ability to activate benzophenone, significant dose-related increases in *umu* gene expression were seen in TA1535/pSK1002 (Takemoto *et al*., 2002); the benzophenone metabolites benzhydrol and *p*-benzoylphenol were also activated by human P450s to produce an increase in *umu* gene expression in this test system. The positive results reported for benzophenone in the *umu* gene expression assay do not directly conflict with the negative results obtained in *Salmonella* gene mutation assays because the endpoints measured by the two assays differ, as do important aspects of the test protocols. Briefly, the *umu* assay indirectly detects DNA damage induced anywhere in the *Salmonella* genome by analyzing fluorescent signals produced by expression of the *umu*-beta-galactosidase gene complex carried in the pSK1002 plasmid (genes in the *umu* operon control SOS error-prone DNA repair which is expressed in response to induced damage). The *Salmonella* assay, in contrast, measures fixed damage induced specifically within defined regions of the histidine operon, resulting in heritable changes in the bacterial DNA directly observable as mutant colonies. Primary DNA damage, such as that detected in the *umu* assay, may or may not result in mutation. In addition to the endpoint differences, the activation systems contained different liver enzyme mixtures, and the human

cytochrome preparations used in the *umu* assay had specific enzymatic cofactors added to the mixture to ensure the availability of a sufficient number of electrons for metabolic activities to proceed. The pretreatments used to induce rodent S9 liver enzymes in standard bacterial mutation assays may not induce the P450 2A6 and specific other cytochromes that were shown to be effective in transforming benzophenone into a DNA-damaging agent in the *umu* assay.

STUDY RATIONALE

Benzophenone is a component of many widely used commercial products, such as plastics and pharmaceutical products, and it is used as a flavor ingredient. It was nominated by the National Institute of Environmental Health Sciences for toxicity and carcinogenicity testing based on the potential for occupational and consumer exposure and the lack of chronic toxicity data. The results of subchronic toxicity studies of benzophenone have been published (NTP, 2000). This report describes the results of 2-year toxicity and carcinogenicity studies conducted in male and female F344/N rats and B6C3F_1 mice, along with toxicokinetic studies (Appendix J). Feed was chosen as the route of exposure because this mimics exposure to humans consuming benzophenone as a flavoring agent. The highest dose was set at 1,250 ppm based on the minimum toxicity observed at this level in the 14-week studies.

MATERIALS AND METHODS

Procurement and Characterization of Benzophenone

Benzophenone was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (10803KG) that was used in the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and the study laboratory, Battelle Columbus Operations (Columbus, OH) (Appendix F). Reports on analyses performed in support of the benzophenone studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white crystal with a geranium- or rose-like odor, was identified as benzophenone by melting point determination; infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy; x-ray crystallography; and low and high resolution mass spectrometry. Karl Fischer titration indicated a moisture content of 0.426%. Gas chromatography indicated one major peak that accounted for 100% of the total peak area. The overall purity of lot 10803KG was determined to be greater than 99%.

To ensure stability, the bulk chemical was stored at approximately 25° C in sealed, amber-glass containers. The study laboratory performed periodic purity reanalyses of the bulk chemical using gas chromatography. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared at least once a month by mixing benzophenone with feed (Table F1). Formulations were stored in five-gallon, white plastic buckets lined with plastic can liners at approximately 5° C for up to 35 days.

Homogeneity studies of the 312 and 1,250 ppm dose formulations and stability studies of the 312 ppm dose formulation were performed by the analytical chemistry laboratory using high performance liquid chromatography (HPLC). Homogeneity was confirmed, and stability was confirmed for at least 35 days for dose formulations stored in sealed glass containers protected from light at up to 5° C. Under simulated animal room dosing conditions, there were small losses after 3 days and significant losses after 7 days. To confirm these findings, the study laboratory performed simulated animal room stability studies of the 312 and 1,250 ppm dose formulations using HPLC. Results indicated that feeder changes twice weekly should be acceptable, though there would be a slight decrease in concentration of benzophenone.

Periodic analyses of the dose formulations of benzophenone were conducted by the study laboratory using HPLC. During the 2-year studies, the dose formulations were analyzed at least every 11 weeks (Table F2). Of the dose formulations analyzed and used, all 63 for rats and all 60 for mice were within 10% of the target concentrations. Animal room samples of these dose formulations were also analyzed; 11 of 24 samples analyzed for rats and 8 of 48 samples analyzed for mice were within 10% of target concentrations. The decline in benzophenone concentration was not anticipated from animal room simulations with air and light performed during pre-study developmental work. After the decline was observed, additional experiments were performed in which benzophenone feed formulations were spiked with rodent urine and feces. Declines were approximately 5% with light and air and increased to approximately 15% in the presence of urine and feces. Contamination occurs when the animals crawl into or onto the feeders. The problem increases in cages where multiple animals are housed and are worst with female mice. Feeders were changed twice per week during the study to minimize the problem, but some contamination was unavoidable.

2-YEAR STUDIES

Study Design

Core study groups of 50 male and 50 female rats and mice were fed diets containing 0, 312, 625, or 1,250 ppm benzophenone for 105 weeks. The highest dose was set at 1,250 ppm based on the minimal toxicity observed at this level in the 14-week studies (NTP, 2000). In the 14-week study, body weight gain was reduced by 12% in female rats exposed to 2,500 ppm benzophenone. Because of the body weight reduction, 1,250 ppm was selected as the high dose for female rats in the 2-year study. This dose was also selected as the high dose for male rats because exposure to 2,500 ppm benzophenone for 14 weeks caused a 7% reduction in body weight gain, significant increases in liver weights (males 43%, females 28%), and increased incidences of kidney lesions. In mice, exposure to 2,500 ppm benzophenone for 14 weeks caused dramatic increases in liver weights (males 55%, females 56%). Therefore, 1,250 ppm benzophenone was also selected as the high dose for the 2-year study in mice.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were 4 weeks old. Animals were quarantined for 11 or 12 days (rats) or 25 or 26 days (mice). Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats were approximately 6 weeks old and mice were approximately 8 weeks old on the first day of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix I).

Animal Maintenance

Rats were housed 2 or 3 (males) or 5 (females) per cage, and mice were housed 1 (male) or 5 (females) per cage. Feed and water were available *ad libitum*. Feed consumption was measured one week out of every four weeks beginning the first week of the study. Cages were changed twice weekly, and cages and racks were rotated every 2 weeks. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix H.

Clinical Examinations and Pathology

Animals were observed twice daily and were weighed initially, on day 8, at 4-week intervals thereafter, and at the end of the studies. Clinical findings were recorded on day 36 and at 4-week intervals (rats had one interval each at 3 and 5 weeks; mice had one interval each at 2, 3, 5, or 6 weeks).

Complete necropsies and microscopic examinations were performed on all core study rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. To perform an extended evaluation of renal tubule proliferative lesions, additional sections of both kidneys in the residual formalin-fixed wet tissues from each male and female rat were embedded in separate paraffin blocks and step sectioned at 1 mm intervals. Up to eight step sections were examined for each animal. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy; the slide and tissue counts were verified; and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney and liver of rats and the kidney, liver, nose, and uterus of mice. Slides of spleen, liver, and lung were graded for severity of mononuclear cell leukemia. Stomach, heart, adrenal gland, and parathyroid gland of male rats and ovary, bone marrow, lung, and mammary gland of female rats were reviewed. Spleen of male and female mice, testes and preputial gland of male mice, and bone marrow and thymus of female mice were reviewed.

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

During the microscopic evaluations of the additional kidney sections for renal tubule proliferative lesions, the step section lesions were compared with lesions observed during the initial standard evaluation to ensure consistency between evaluations and prevent duplication of diagnoses for lesions already diagnosed in the standard evaluations. The findings and slides from the step section evaluations were reviewed by the PWG chairperson using procedures for the reviews of standard sections. Final diagnoses for the step sections were recorded separately from the standard sections.

TABLE 4
Experimental Design and Materials and Methods in the 2-Year Feed Studies of Benzophenone

Study Laboratory
Battelle Columbus Operations (Columbus OH)

Strain and Species
F344/N rats
$B6C3F_1$ mice

Animal Source
Taconic Laboratory Animals and Services (Germantown, NY)

Time Held Before Studies
Rats: 11 (males) or 12 days (females)
Mice: 26 (males) or 25 days (females)

Average Age When Studies Began
Rats: 6 weeks
Mice: 8 weeks

Date of First Exposure
Rats: August 16 (males) or August 17 (females), 1999
Mice: September 14 (males) or September 13 (females), 1999

Duration of Exposure
105 weeks

Date of Last Exposure
Rats: August 13 or 14 (males) or August 14, 15, or 16 (females), 2001
Mice: September 12, 13, or 14 (males) or September 10, 11, or 12 (females), 2001

Necropsy Dates
Rats: August 13 or 14 (males) or August 14, 15, or 16 (females), 2001
Mice: September 12, 13, or 14 (males) or September 10, 11, or 12 (females), 2001

Average Age at Necropsy
Rats: 110 weeks
Mice: 112 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
Rats: 2 or 3 (males) or 5 (females)
Mice: 1 (males) or 5 (females)

Method of Animal Identification
Tail tattoo

Diet
NTP-2000 irradiated open formula meal (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed twice weekly

Water
Tap water (City of Columbus) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

TABLE 4
Experimental Design and Materials and Methods in the 2-Year Feed Studies of Benzophenone

Cages
Polycarbonate (Lab Products, Inc., Seaford, DE), changed twice weekly, rotated every 2 weeks

Bedding
Irradiated Sani-Chips® (P.J. Murphy Forest Products Corp., Montville, NJ), changed at least twice weekly

Cage Filters
DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH), changed every two weeks

Racks
Stainless steel (Lab Products, Inc., Seaford, DE), changed and rotated every 2 weeks

Animal Room Environment
Temperature: 72° ± 3° F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Exposure Concentrations
0, 312, 625, or 1,250 ppm in feed

Type and Frequency of Observation
Observed twice daily. Animals were weighed initially, on day 8, at 4-week intervals thereafter, and at the end of the studies. Clinical findings were recorded on day 36 and at 4-week intervals (rats had one interval at 3 and 5 weeks; mice had one interval each at 2, 3, 5 or 6 weeks) throughout the study. Feed consumption was recorded for 1 week out of every 4 weeks beginning the first week of the study.

Method of Sacrifice
CO_2 inhalation

Necropsy
Necropsies were performed on all animals.

Histopathology
Complete histopathology was performed on rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eyes, harderian gland, gallbladder (mice only), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver (2 sections including left lateral lobe and median lobe), lung, lymph nodes (mandibular and mesenteric), mammary gland with adjacent skin, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic

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

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The current NTP historical database contains all 23 studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison.

Quality Assurance Methods

The 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in

the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of benzophenone was assessed by testing the ability of benzophenone to induce mutations in various strains of *Salmonella typhimurium,* micronucleated erythrocytes in mouse bone marrow, and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database, permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 2). Survival of 1,250 ppm males was significantly less than that of the control group. Survival of exposed females was similar to that of the controls.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of 1,250 ppm males were less than those of the controls after week 62, and those of 625 ppm males were less after week 86 (Figure 3 and Table 6). Mean body weights of 625 and 1,250 ppm female rats were generally less than those of the controls after week 10 (Figure 3 and Table 7). Feed consumption by 1,250 ppm males was less than that by the controls after week 70 of the study; feed consumption by

TABLE 5
Survival of Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	25	12	16	44
Natural deaths	3	11	3	4
Animals surviving to study termination	22	27	31	2
Percent probability of survival at end of study[a]	44	54	62	4
Mean survival (days)[b]	681	674	694	622
Survival analysis[c]	P<0.001	P=0.517N	P=0.099N	P<0.001
Female				
Animals initially in study	50	50	50	50
Moribund	16	10	9	13
Natural deaths	2	2	4	3
Animals surviving to study termination	32	38	37	34
Percent probability of survival at end of study	64	76	74	68
Mean survival (days)	688	715	713	704
Survival analysis	P=0.985N	P=0.246N	P=0.354N	P=0.809N

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

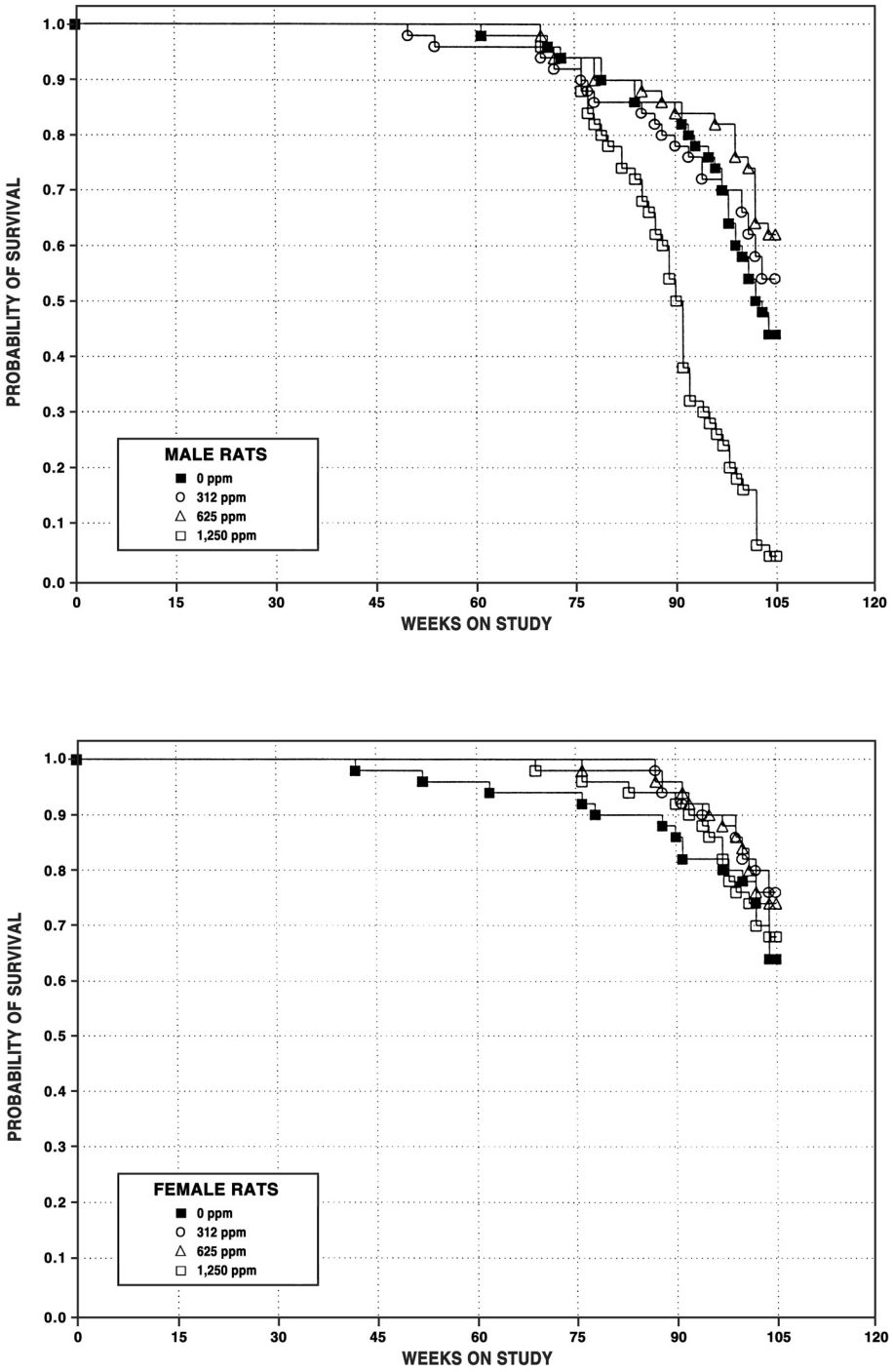


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Benzophenone in Feed for 2 Years

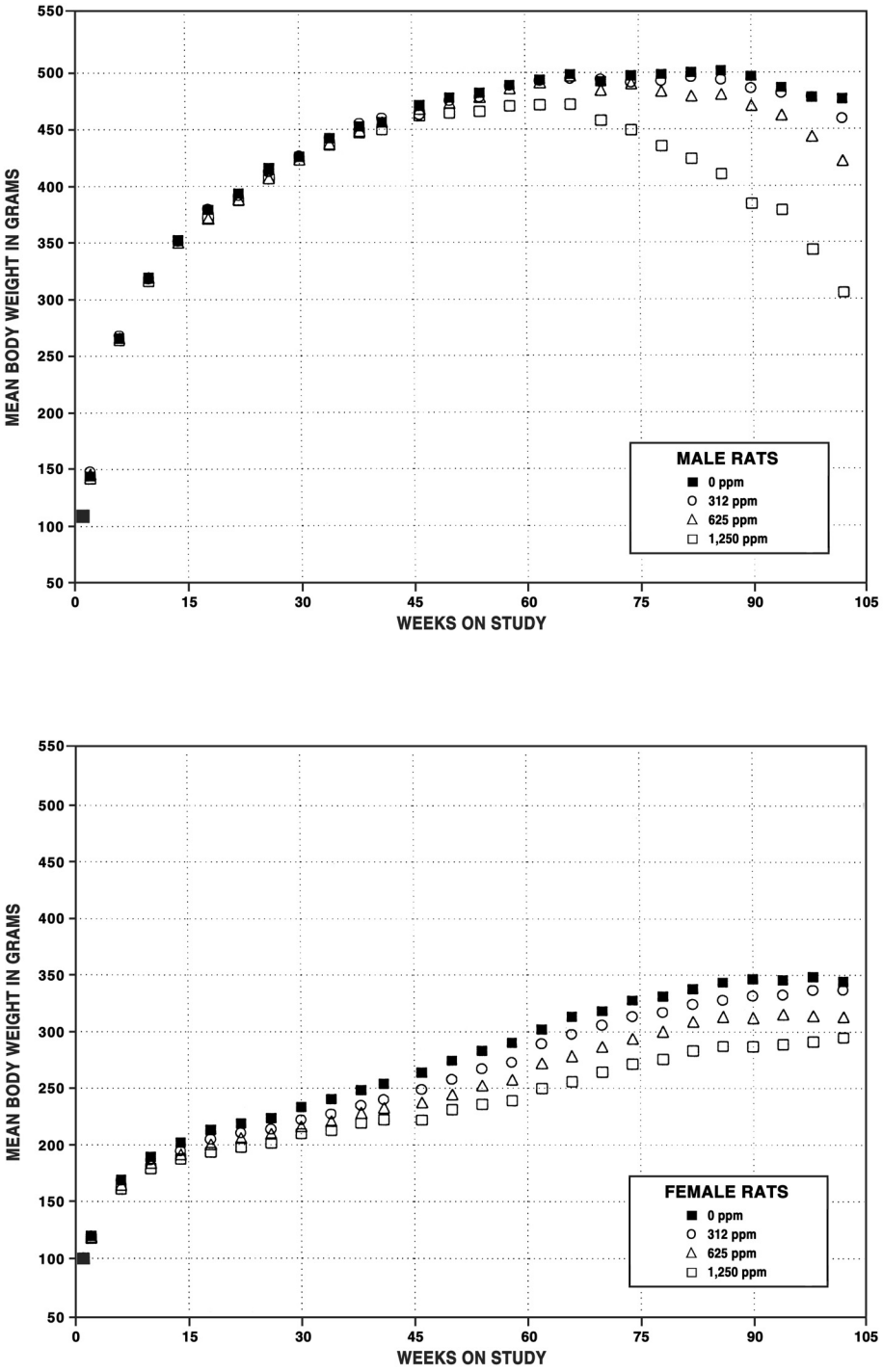


FIGURE 3
Growth Curves for Male and Female Rats Exposed to Benzophenone in Feed for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of Benzophenone

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	108	50	109	101	50	109	100	50	110	102	50
2	144	50	148	103	50	146	101	50	142	99	50
6	266	50	268	101	50	266	100	50	264	99	50
10	319	50	318	100	50	319	100	50	316	99	50
14	352	50	352	100	50	350	100	50	353	100	50
18	379	50	380	100	50	372	98	50	372	98	50
22	394	50	392	99	50	388	99	50	388	99	50
26	416	50	413	99	50	407	98	50	407	98	50
30	426	50	427	100	50	424	99	50	423	99	50
34	442	50	443	100	50	438	99	50	436	99	50
38	453	50	455	101	50	449	99	50	447	99	50
41	457	50	460	101	50	457	100	50	450	99	50
46	472	50	463	98	50	468	99	50	462	98	50
50	478	50	476	100	50	473	99	50	465	97	50
54	482	50	479	99	49	479	99	50	466	97	50
58	489	50	488	100	48	486	99	50	471	96	50
62	494	49	493	100	48	491	100	50	472	96	50
66	499	49	495	99	48	497	100	50	472	95	50
70	492	49	494	100	47	485	98	50	458	93	50
74	498	47	491	99	46	490	99	47	449	90	47
78	499	47	493	99	44	484	97	47	436	87	42
82	500	45	496	99	43	479	96	45	424	85	39
86	502	43	494	98	42	481	96	44	411	82	34
90	497	43	486	98	40	471	95	43	384	77	27
94	487	39	482	99	38	463	95	42	379	78	16
98	478	34	478	100	35	444	93	41	343	72	11
102	477	27	460	96	31	422	89	37	306	64	8
Mean for weeks											
1-13	209		211	101		210	100		208	100	
14-52	427		426	100		423	99		420	98	
53-102	492		487	99		475	97		421	86	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of Benzophenone

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	101	50	101	100	50	100	99	50	100	99	50
2	120	50	120	100	50	119	99	50	118	98	50
6	169	50	169	100	50	165	97	50	161	95	50
10	189	50	186	98	50	184	97	50	179	95	50
14	202	50	195	96	50	191	95	50	187	93	50
18	214	50	205	96	50	201	94	50	193	91	50
22	219	50	210	96	50	206	94	50	198	90	50
26	224	50	214	96	50	210	94	50	202	90	50
30	234	50	222	95	50	216	93	50	210	90	50
34	241	50	227	95	50	221	92	50	213	89	50
38	249	50	235	95	50	228	92	50	219	88	50
41	254	50	240	95	50	233	92	50	222	88	50
46	264	49	249	94	50	237	90	50	222	84	50
50	275	49	258	94	50	245	89	50	231	84	50
54	283	48	268	95	50	253	89	50	236	83	50
58	290	48	273	94	50	258	89	50	239	82	50
62	302	48	290	96	50	272	90	50	250	83	50
66	313	47	298	95	50	279	89	50	256	82	50
70	318	47	306	96	50	287	90	50	265	83	49
74	328	47	313	96	50	294	90	50	272	83	49
78	331	46	317	96	50	300	91	49	276	83	48
82	338	45	324	96	50	309	92	49	284	84	48
86	344	45	328	95	50	313	91	49	287	84	47
90	347	43	332	96	47	312	90	48	287	83	46
94	346	41	333	96	46	315	91	46	289	84	45
98	349	40	337	97	45	314	90	44	291	84	41
102	345	37	337	98	41	313	91	40	295	86	37
Mean for weeks											
1-13	145		144	99		142	98		140	97	
14-52	238		226	95		219	92		210	88	
53-102	326		312	96		294	90		271	83	

1,250 ppm females was generally less than that by the controls throughout the study (Tables G1 and G2, respectively). Dietary concentrations of 312, 625, and 1,250 ppm resulted in average daily doses of approximately 15, 30, and 60 mg benzophenone/kg body weight to males and 15, 30, and 65 mg/kg to females. No clinical findings other than those associated with morbidity (e.g., nasal/eye discharge, thinness, ruffled fur) were attributed to benzophenone exposure.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and histiocytic sarcoma and neoplasms and/or nonneoplastic lesions of the kidney, liver, thyroid gland, mammary gland, and skin. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Kidney: Initially, the standard single sections of the left and right kidneys from each rat were examined microscopically. There was a positive trend in the incidences of renal tubule adenoma in males (Tables 8 and A3). No renal tubule adenomas have been reported in feed study controls given NTP-2000 diet, with a single exception found in this study. The incidences in 625 and 1,250 ppm males exceeded the historical range in controls from all routes (Tables 8 and A4a). One renal tubule carcinoma was observed in a 312 ppm male rat. These renal tubule neoplasms were accompanied by significantly increased incidences of renal tubule hyperplasia in 625 and 1,250 ppm males (Tables 8 and A5). Two females in the 625 ppm group and one in the 1,250 ppm group had renal tubule adenomas; this neoplasm has occurred in only one historical feed control female (Tables 8, B1, and B4a). Renal tubule hyperplasia was not significantly increased in exposed females. Renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions of the renal tubule epithelium. Because the incidences of renal tubule adenoma in exposed males and females and renal tubule hyperplasia in males were increased in the single sections, additional kidney sections were evaluated. After the extended evaluation (Tables 8, A3, and B3), a significant increase in the incidence of renal tubule adenoma was observed in 1,250 ppm males, and increased incidences of hyperplasia were observed in all exposed groups of males. As a result of the extended evaluation, three renal tubule adenomas were observed in the control females; no additional neoplasms were observed in exposed females. Incidences of renal tubule hyperplasia in all exposed female groups were significantly greater than that of the control group when the single and step section evaluations were combined (Table 8).

Renal tubule hyperplasia consisted of one or more tubules having multiple layers of polygonal epithelial cells with slightly varied sizes. Nuclei were generally round, stained slightly basophilic, and had prominent nucleoli. The cytoplasm was clear, eosinophilic or basophilic with a granular to foamy appearance. Cystic and solid patterns were formed. Hyperplastic tubules with lumens partially or totally filled by epithelial cells were enlarged two to four times normal diameter. Renal tubule adenomas were larger, discrete lesions, ranging from greater than four tubule diameters to 1 mm or more in size. They often consisted of a solid mass of large, relatively normal appearing, closely packed tubular epithelial cells. Cells within adenomas were mildly to moderately pleomorphic, sometimes had vacuolated cytoplasm, and tended to form complex patterns, particularly microtubular structures. The renal tubule carcinoma was differentiated from the adenomas in that it was larger, had a prominent vascular supply, and had more anaplasia and cellular atypia. Cells of this carcinoma were characterized by vesiculated nuclei with prominent nucleoli and increased numbers of mitotic figures.

Oncocytic hyperplasia was observed in the single sections of one male exposed to 625 ppm. During the extended evaluation, this lesion was observed in a few additional exposed male rats (Tables 8 and A5). This lesion was characterized by individual tubules or small clusters of tubules that were somewhat dilated and totally filled by large polygonal cells with abundant, brightly eosinophilic granular or reticulated cytoplasm and small, centrally located, basophilic nuclei (oncocytes). These lesions are thought to arise from the distal tubule epithelium. One male exposed to 1,250 ppm had a benign oncocytic neoplasm (oncocytoma) at the extended evaluation.

Significantly increased incidences of pelvic transitional epithelial hyperplasia were observed in all exposed male

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Renal Tubule, Hyperplasia[a]	1 (1.0)[b]	5 (1.4)	20** (1.5)	23** (1.3)
Renal Tubule, Hyperplasia, Oncocytic	0	0	1 (2.0)	0
Pelvis, Transitional Epithelium, Hyperplasia	1 (1.0)	11** (1.2)	29** (1.5)	34** (1.7)
Nephropathy	50 (1.3)	45 (2.4)▲	50 (3.3)▲	50 (3.8)▲
Renal Tubule, Cyst	0	0	1	9**
Pelvis, Transitional Epithelium, carcinoma	0	0	0	1
Renal Tubule, Adenoma[c]				
Overall rate[d]	1/50 (2%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate[e]	2.4%	2.4%	4.5%	12.1%
Terminal rate[f]	0/22 (0%)	1/27 (4%)	1/31 (3%)	0/2 (0%)
First incidence (days)	709	729 (T)	687	537
Poly-3 test[g]	P=0.046	P=0.758	P=0.519	P=0.114
Renal Tubule, Carcinoma	0	1	0	0
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	2 (1.0)	8* (1.1)	26** (2.0)	37** (2.2)
Renal Tubule, Hyperplasia, Oncocytic	0	1 (1.0)	3 (1.3)	1 (2.0)
Oncocytoma	0	0	0	1
Renal Tubule, Adenoma				
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted rate	2.4%	2.4%	11.2%	12.1%
Terminal rate	0/22 (0%)	1/27 (4%)	4/31 (13%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	624
Poly-3 test	P=0.034	P=0.757	P=0.114	P=0.113
Renal Tubule, Carcinoma	0	1	0	0
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	3 (1.0)	11* (1.3)	30** (1.8)	40** (2.1)▲
Renal Tubule, Hyperplasia, Oncocytic	0	1 (1.0)	4 (1.5)	1 (2.0)
Oncocytoma	0	0	0	1
Pelvis, Transitional Epithelium Carcinoma	0	0	0	1
Renal Tubule, Adenoma				
Overall rate	2/50 (4%)	2/50 (4%)	7/50 (14%)	8/50 (16%)
Adjusted rate	4.7%	4.8%	15.6%	23.3%
Terminal rate	0/22 (0%)	2/27 (7%)	5/31 (15%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	537
Poly-3 test	P=0.004	P=0.688	P=0.093	P=0.017
Renal Tubule, Carcinoma	0	1	0	0

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm		625 ppm		1,250 ppm	
Female								
Number Examined Microscopically	50		50		50		50	
Single Sections (Standard Evaluation)								
Renal Tubule, Hyperplasia	0		1	(4.0)	1	(3.0)	1	(4.0)
Pelvis, Transitional Epithelium, Hyperplasia	1	(1.0)	2	(1.5)	2	(2.0)	4	(1.0)
Nephropathy	47	(1.1)	49	(1.4)	48	(1.7)▲	49	(2.0)▲
Renal Tubule, Adenoma, Multiple[h]	0		0		2		1	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	1	(1.0)	7*	(1.1)	9*	(2.1)	6	(1.7)
Renal Tubule, Adenoma	3		0		2		1	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	1	(1.0)	8*	(1.5)	10**	(2.2)	7*	(2.0)
Renal Tubule, Adenoma, Multiple	0		0		1		1	
Renal Tubule, Adenoma (includes multiple)	3		0		2		1	

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
▲ Significantly different ($P \leq 0.05$) from the control group by the Mann-Whitney U test
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year feed studies with controls given NTP-2000 diet (mean ± standard deviation): 1/459 (0.3% ± 0.8%), range 0%-2%; all routes 5/1,152 (0.5% ± 0.9%), range 0%-2%
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Historical incidence: feed 1/460 (0.1% ± 0.4%), range 0%-1%; all routes 1/1,205 (0.1% ± 0.2%), range 0%-1%

groups; a slight increase in the incidence of this lesion was observed in females exposed to 1,250 ppm (Tables 8, A5, and B5). Hyperplasia of the transitional epithelium lining the pelvis and overlying the renal papilla frequently accompanies severe nephropathy, and the increased incidences in the current study may reflect the enhanced nephropathy. One male exposed to 1,250 ppm had a transitional epithelial carcinoma. Transitional epithelial hyperplasia was characterized by small papillary fronds or nodules of normal appearing transitional epithelial cells protruding into the pelvis lumen.

In males, the severity of chronic nephropathy increased with increasing exposure concentration, and the increases in all exposed groups were significant (Table 8). In exposed females, the severity of nephropathy was significantly increased in the 625 and 1,250 ppm groups. Nephropathy is an age-related disease process characterized by a spectrum of lesions, including varying degrees of tubule dilation; proteinaceous tubule casts; atrophy, degeneration, regeneration, and hypertrophy of the tubule epithelium; thickening of tubule and glomerular basement membrane; glomerulosclerosis; interstitial fibrosis; and varying numbers and aggregates of mononuclear inflammatory cells within the interstitium. Minimal nephropathy was characterized by a few scattered foci of tubule regeneration. These regenerative tubules had increased numbers of more intensely stained basophilic cells. Basement membranes, both in glomeruli and around tubules, were slightly thickened. As nephropathy became more severe, tubule dilatation, proteinaceous casts, and interstitial fibrosis were evident. Severe nephropathy resulted in the formation of renal tubule cysts. The incidence of renal tubule cysts in 1,250 ppm males was significantly greater than that in the control group.

The increased severity of the nephropathy in 1,250 ppm males was associated with decreased survival after 80 weeks on study. Twenty-eight of 48 early deaths (58%) in this group, many moribund sacrificed, were attributed to nephropathy caused by benzophenone exposure. Because of the severe nephropathy, increases in several other findings usually associated with uremia were observed at multiple sites in male rats. These secondary findings included increased mineralization of blood vessels and basement membranes, including kidney cortex, heart, seminal vesicles, forestomach, glandular stomach, and lung, in addition to parathyroid gland hyperplasia and fibrous osteodystrophy in bone (Tables 9 and A5).

All Organs: Increased incidences of mononuclear cell leukemia occurred in exposed groups of females, and the difference from the control group was significant at 625 ppm (Tables 10, 11, and B3). Male rats exposed to 312 or 625 ppm also had significantly increased incidences of mononuclear cell leukemia, although that of 1,250 ppm males was slightly decreased (Tables 10, 11, and A3). The incidences in all exposed groups of females and 312 and 625 ppm males exceeded the range reported for historical controls from feed studies (Tables 10, B4b, and A4b).

The mononuclear cell leukemia in female and male rats in the control and dosed groups was classified according to the extent of involvement of the spleen, liver, lung, and other organs. Similar criteria have been used for previous NTP studies (NTP, 1986). In stage 1, the spleen was not enlarged or was only slightly enlarged with small numbers of neoplastic mononuclear cells in the red pulp; none or very few mononuclear cells were observed in the liver sinusoids. No identifiable neoplastic cells were observed in other organs. In stage 2, the spleen was moderately enlarged with moderate to large numbers of neoplastic mononuclear cells in the red pulp; architectural features, including lymphoid follicles and periarteriolar lymphocytic sheaths, remained intact. There was minimal to moderate involvement of the liver. Neoplastic mononuclear cells may have been evident in blood vessels in other organs, but the aggregates/masses of neoplastic cells were generally limited to the spleen and liver. In stage 3, there was advanced disease with multiple organ involvement. The spleen was usually markedly enlarged with an effacement of normal architectural features by accumulated neoplastic mononuclear cells. The liver was moderately to markedly enlarged and nodular; hepatic parenchyma showed variable degenerative changes associated with the accumulation of neoplastic cells. There were accumulations of neoplastic cells in other organs, including the lung, lymph nodes, kidney, brain, and adrenal gland. According to these criteria, the involvement of spleen, liver, and other organs in female rats increased with increased levels of benzophenone exposure (Table B1). The extent of involvement by leukemia in male rats decreased in exposed groups (Tables 10, 11, and A3).

TABLE 9
Incidences of Secondary Lesions Associated with Severe Nephropathy in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Blood Vessel[a]	50	50	50	50
Mineralization[b]	0	1 (1.0)[c]	1 (4.0)	11** (3.1)
Bone	50	50	50	50
Fibrous Osteodystrophy	0	0	1 (2.0)	4* (1.8)
Heart	50	50	50	50
Mineralization	0	0	2 (1.5)	6** (2.3)
Kidney	50	50	50	50
Cortex, Mineralization	0	1 (1.0)	4 (2.5)	14** (2.8)
Lung	50	49	50	50
Mineralization	0	0	2 (2.5)	10** (2.7)
Parathyroid Gland	49	45	48	49
Hyperplasia	2 (1.5)	1 (1.0)	19** (2.0)	32** (2.2)
Seminal Vesicle	50	50	50	49
Mineralization	0	0	0	4* (2.8)
Stomach, Forestomach	50	49	49	50
Mineralization	0	1 (1.0)	1 (2.0)	3 (2.7)
Stomach, Glandular	50	50	49	50
Mineralization	0	0	5* (2.6)	15** (2.7)

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

TABLE 10
Incidences of Mononuclear Cell Leukemia and Histiocytic Sarcoma in Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Males				
Mononuclear Cell Leukemia[a]				
Overall rate[b]	27/50 (54%)	41/50 (82%)	39/50 (78%)	24/50 (48%)
Adjusted rate[c]	55.8%	82.3%	81.2%	59.3%
Terminal rate[d]	6/22 (27%)	20/27 (74%)	25/31 (81%)	2/2 (100%)
First incidence (days)	425	344	494	487
Poly-3 test[e]	P=0.508	P=0.003	P=0.005	P=0.454
Females				
Mononuclear Cell Leukemia[f]				
Overall rate	19/50 (38%)	25/50 (50%)	30/50 (60%)	29/50 (58%)
Adjusted rate	42.3%	51.5%	61.3%	59.6%
Terminal rate	13/32 (41%)	19/38 (50%)	21/37 (57%)	20/34 (59%)
First incidence (days)	637	613	609	480
Poly-3 test	P=0.058	P=0.247	P=0.048	P=0.068
Histiocytic Sarcoma[g]				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	2.1%	4.3%
Terminal rate	0/32 (0%)	0/38 (0%)	0/37 (0%)	0/34 (0%)
First incidence (days)	—[h]	—[i]	528	480
Poly-3 test	P=0.074	—	P=0.516	P=0.251

[a] Historical incidence in 2-year feed studies with controls given NTP-2000 diet (mean ± standard deviation): 231/460 (49.1% ± 11.9%), range 30%-68%; all routes 514/1,159 (43.1% ± 12.8%), range 22%-68%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[f] Historical incidence: feed 112/460 (24.6% ± 9.5%), range 12%-38%; all routes 330/1,209 (28.0% ± 11.2%), range 12%-52%
[g] Historical incidence: feed 0/460; all routes 1/1,209 (0.1% ± 0.4%), range 0%-2%
[h] Not applicable; no neoplasms in animal group
[i] Value of statistic cannot be computed

TABLE 11
Incidences and Stages of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Males				
Number surviving at end of study	22	27	31	2
Number with grade 1 mononuclear cell leukemia	1	8	7	11
Number with grade 2 mononuclear cell leukemia	4	8	18	2
Number with grade 3 mononuclear cell leukemia	22	25	14	11
Total with mononuclear cell leukemia	27	41	39	24
Average staging grade	2.8	2.4*	2.2**	2.0**
Females				
Number surviving at end of study	32	38	37	34
Number with grade 1 mononuclear cell leukemia	10	13	11	10
Number with grade 2 mononuclear cell leukemia	6	4	7	8
Number with grade 3 mononuclear cell leukemia	3	8	12	11
Total with mononuclear cell leukemia	19	25	30	29
Average staging grade	1.6	1.8	2.0	2.0

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$

A few histiocytic sarcomas occurred in the 625 and 1,250 ppm groups of females (Table 10). This neoplasm has not been observed in historical feed study controls given NTP-2000 diet and has been observed in only one out of 1,209 historical controls for all routes (Tables 10 and B4b). Histiocytic sarcomas were observed in the lung and livers of all three affected rats. Histologically, the histiocytic sarcomas in these rats had several characteristic microscopic features. The neoplastic cells had typical histiocytic appearances with relatively abundant, pale eosinophilic cytoplasm. Their dark basophilic nuclei were oval to elongated with small or inconspicuous nucleoli. Variation in the size and shape of these neoplastic cells and high cytoplasmic-to-nuclear ratios were observed. Another characteristic histologic feature observed in two rats consisted of necrotic areas surrounded by rows of neoplastic cells. Prominent multi-nucleated giant cells were present in two animals. Fibrosis varied from minimal to extensive in one rat. Growth was both infiltrative and expansive and extended on pleural and peritoneal surfaces. Histologic features differed from animal to animal and from site to site in the same animal. Neoplastic histiocytic cells infiltrated the liver, diffusely expanding the hepatic parenchyma (Plate 1). In the lung, intravascular masses and perivascular infiltrates of neoplastic histiocytic cells were observed in all affected rats (Plate 2). Two of the three rats had moderate to marked accumulation of hyaline droplets in their kidneys, another finding consistent with histiocytic sarcomas.

Liver: The incidences of centrilobular hepatocellular hypertrophy in all exposed groups of males and females were significantly greater than those in the control groups (Tables 12, A5, and B5). This hepatocellular hypertrophy is consistent with the induction of P450 enzymes previously observed in the 14-week study (NTP, 2000). Incidences of cystic degeneration of hepatocytes and chronic active inflammation in 625 and 1,250 ppm males and bile duct hyperplasia in all exposed groups of females were significantly greater than those in the control groups. The incidences of chronic active inflammation in all exposed female groups were significantly decreased.

Thyroid Gland: The incidences of C-cell hyperplasia were significantly decreased in all exposed groups of males and females (Tables 12, A5, and B5). Increased thyroid gland C-cell hyperplasia is an age-associated

TABLE 12
Incidences of Selected Nonneoplastic Lesions in Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Liver[a]	50	50	50	50
Hepatocyte, Centrilobular, Hypertrophy[b]	0	17** (1.3)[c]	31** (1.8)	19** (1.5)
Degeneration, Cystic	8 (1.3)	11 (1.0)	20** (1.3)	15* (1.2)
Inflammation, Chronic Active	22 (1.9)	21 (1.6)	35** (1.9)	33* (1.8)
Thyroid gland	50	50	50	50
C-Cell Hyperplasia	17 (2.0)	8* (2.0)	8* (2.1)	5* (1.4)
Female				
Liver	50	50	50	50
Hepatocyte, Centrilobular, Hypertrophy	0	27** (1.0)	30** (1.3)	33** (2.0)
Bile duct, Hyperplasia	10 (1.3)	35** (1.2)	39** (1.4)	40** (1.6)
Inflammation, Chronic Active	46 (1.5)	38* (1.5)	29** (1.3)	30** (1.4)
Thyroid gland	50	50	50	50
C-Cell Hyperplasia	34 (1.8)	11** (1.8)	13** (1.7)	8** (1.9)

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

change in rats (Boorman *et al.*, 1996). Therefore, this decrease appears to be treatment related.

Mammary Gland: Statistically significant decreases in the incidences of fibroadenoma (including multiple) occurred in females exposed to 625 or 1,250 ppm benzophenone (0 ppm, 27/50; 312 ppm, 24/50; 625 ppm, 15/50; 1,250 ppm, 7/50; Table B3). Multiple fibroadenomas were significantly decreased in the 1,250 ppm group (6/50; 4/50; 3/50; 0/50; Table B1). The incidence of fibroadenoma (including multiple) combined in the 1,250 ppm group is fewer than expected after adjusting for decreased body weight (14.7 expected, 7 observed) and is less than the historical control range from feed studies and from all routes combined [feed: 213/460 (44% ± 12%), range 28%-55%; all routes: 567/1,209 (46% ± 12%), range 28%-72%].

Skin: The incidences of keratoacanthoma were decreased in all exposed male groups, and the differences from the control group incidence were significant at 312 and 625 ppm (10/50; 3/50; 3/50; 3/50; Table A3). The incidence in the control group was the highest observed in historical controls in recent studies, whereas the exposed group incidences were within the historical ranges [feed: 34/460 (8% ± 6%), range 2%-20%; all routes: 69/1,159 (6% ± 4%), range 0%-20%]. Therefore, the decreased incidences were not considered to be related to benzophenone exposure.

MICE
2-YEAR STUDY
Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 13 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed groups of mice was similar to that of the control groups, except in 1,250 ppm females where there was decreased survival toward the end of the study. However, this decrease was not statistically significant.

Body Weights, Feed and Compound Consumption, and Clinical Findings

Mean body weights of exposed groups of males were similar to those of the controls throughout the study (Table 14 and Figure 5). Mean body weights of 1,250 ppm females were less than those of the controls after week 37; those of 625 ppm females were less during year 2 of the study; and those of 312 ppm females were less after week 86 (Table 15 and Figure 5). Feed consumption by exposed males and females was similar to that by the controls throughout the study (Tables G3

TABLE 13
Survival of Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	5	3	5	2
Natural deaths	1	3	1	3
Animals surviving to study termination	44	44	44	45
Percent probability of survival at end of study[a]	88	88	88	90
Mean survival (days)[b]	717	713	721	722
Survival analysis[c]	P=0.825N	P=1.000	P=1.000N	P=0.977N
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	0	0	0	1
Moribund	4	2	5	6
Natural deaths	6	6	4	12
Animals surviving to study termination	40	42	41	31
Percent probability of survival at end of study	80	84	82	63
Mean survival (days)	706	707	704	685
Survival analysis	P=0.032	P=0.813N	P=0.992N	P=0.107

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

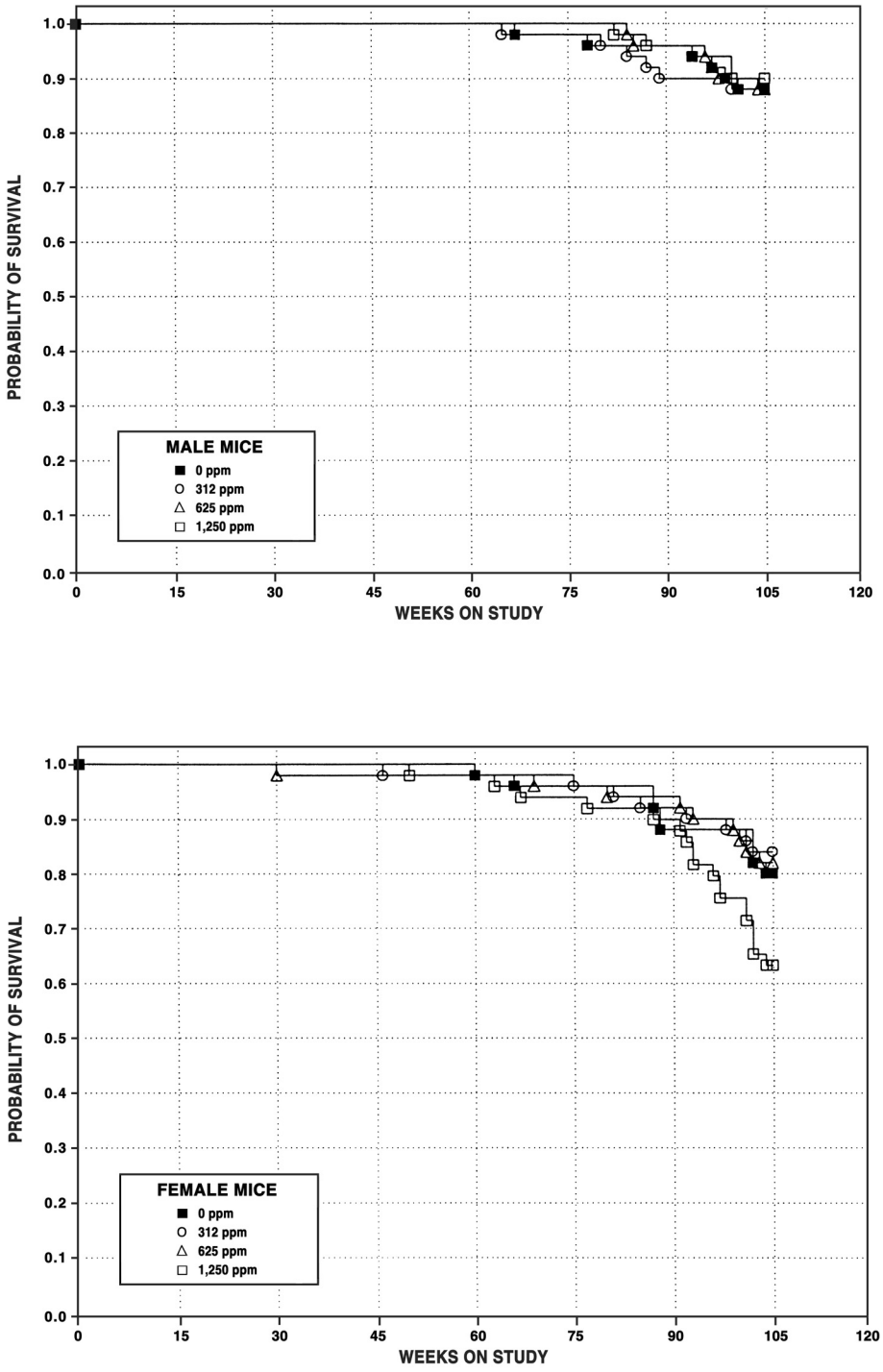


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Benzophenone in Feed for 2 Years

TABLE 14
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of Benzophenone

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.3	50	23.1	99	50	22.9	98	50	23.3	100	50
2	23.9	50	24.2	101	50	23.9	100	50	24.0	100	50
3	25.2	50	24.6	98	50	25.0	99	50	25.1	100	50
6	28.5	50	28.7	101	50	28.5	100	50	28.3	99	50
10	32.0	50	31.8	99	50	31.7	99	50	31.3	98	50
14	34.9	50	34.4	99	50	35.3	101	50	33.9	97	50
18	37.4	50	37.5	100	50	36.9	99	50	35.9	96	50
22	38.9	50	38.0	98	50	38.5	99	50	38.3	99	50
26	40.9	50	40.2	98	50	41.0	100	50	40.6	99	50
30	41.6	50	41.3	99	50	41.6	100	50	41.4	100	50
34	43.1	50	42.9	100	50	41.6	97	50	41.9	97	50
37	43.6	50	43.3	99	50	42.9	98	50	42.2	97	50
42	44.6	50	43.9	98	50	44.1	99	50	43.2	97	50
46	45.0	50	44.4	99	50	44.0	98	50	43.6	97	50
50	46.0	50	45.8	100	50	45.0	98	50	45.0	98	50
54	45.7	50	44.9	98	50	44.1	97	50	44.6	98	50
58	45.9	50	44.7	97	50	44.4	97	50	45.6	99	50
62	45.9	50	44.7	97	50	45.4	99	50	45.8	100	50
66	44.1	50	44.8	102	49	45.4	103	50	45.3	103	50
70	43.8	49	44.3	101	49	44.8	102	50	44.7	102	50
74	44.0	49	45.0	102	49	44.9	102	50	45.2	103	50
78	43.1	48	44.1	102	49	44.5	103	50	43.8	102	50
84	40.7	48	40.8	100	48	40.9	101	50	40.4	99	49
86	41.7	48	41.5	100	47	42.2	101	48	41.3	99	49
90	41.9	48	41.7	100	45	41.7	100	48	41.3	99	48
94	41.4	48	40.8	99	45	41.0	99	48	39.8	96	48
98	41.2	46	39.8	97	45	40.3	98	46	39.5	96	47
102	40.3	44	39.5	98	44	40.3	100	45	38.4	95	45
Mean for weeks											
1-13	26.6		26.5	100		26.4	99		26.4	99	
14-52	41.6		41.2	99		41.1	99		40.6	98	
53-102	43.1		42.8	99		43.1	100		42.7	99	

TABLE 15
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of Benzophenone

Weeks on Study	0 ppm		312 ppm			625 ppm			1,250 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.8	50	18.6	99	50	18.6	99	50	18.5	98	50
2	19.1	50	19.5	102	50	18.6	97	50	19.5	102	50
6	22.5	50	22.4	100	50	22.7	101	50	22.8	101	50
10	25.0	50	25.7	103	50	24.0	96	50	25.7	103	50
14	27.2	50	28.4	104	50	26.9	99	50	28.0	103	50
18	29.5	50	30.8	104	50	30.3	103	50	30.3	103	50
22	32.8	50	33.7	103	50	33.3	102	50	32.2	98	50
26	33.2	50	35.1	106	50	33.6	101	50	33.0	99	50
30	35.3	50	36.6	104	50	35.5	101	50	34.4	98	50
34	36.5	50	38.0	104	50	36.9	101	49	35.1	96	50
37	38.3	50	39.7	104	50	38.0	99	49	36.2	95	50
42	39.8	50	40.6	102	50	39.3	99	49	37.2	94	50
46	41.2	50	42.0	102	49	40.0	97	49	37.2	90	50
50	41.8	50	42.9	103	49	41.1	98	49	37.6	90	50
54	43.3	50	42.8	99	49	41.4	96	49	37.2	86	49
58	43.7	50	43.5	100	49	40.2	92	49	37.8	87	48
62	44.6	49	43.5	98	49	41.4	93	49	37.9	85	48
66	44.4	48	43.1	97	49	41.4	93	49	38.5	87	47
70	44.4	48	43.3	98	49	41.7	94	48	38.9	88	46
74	45.6	48	44.2	97	49	42.2	93	48	39.4	86	46
78	46.2	48	43.8	95	48	41.5	90	48	39.5	86	45
84	43.5	48	41.4	95	47	39.5	91	47	37.4	86	45
86	43.9	48	42.0	96	46	41.0	93	47	37.8	86	45
90	44.4	44	41.1	93	46	40.6	91	47	38.4	87	44
94	44.4	44	41.1	93	45	41.1	93	45	38.6	87	40
98	45.1	44	41.3	92	45	41.4	92	45	38.4	85	37
102	43.5	44	40.4	93	43	40.2	92	42	37.2	86	35
Mean for weeks											
1-13	21.4		21.6	101		21.0	98		21.6	101	
14-52	35.6		36.8	103		35.5	100		34.1	96	
53-102	44.4		42.4	96		41.0	92		38.2	86	

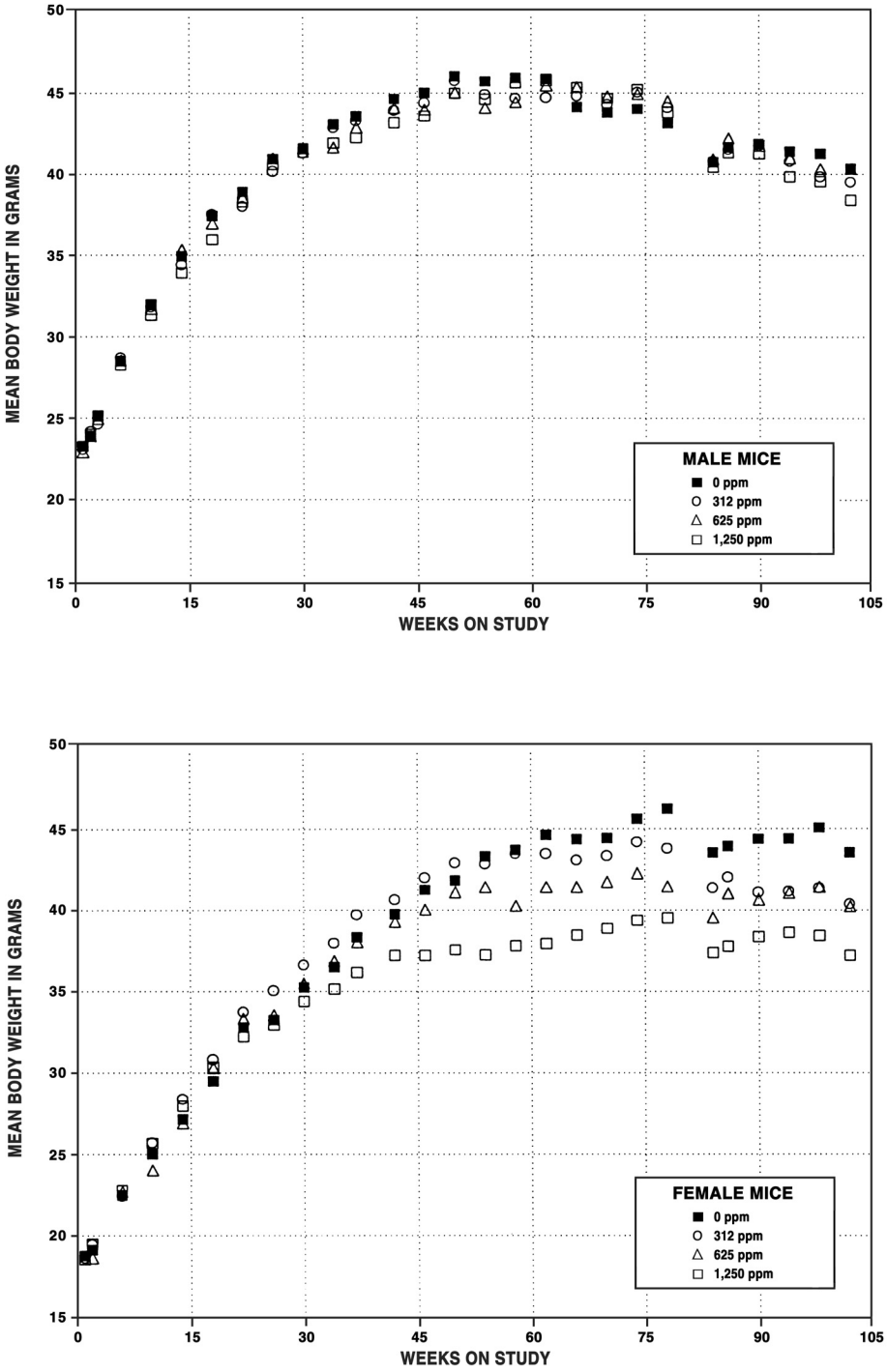


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Benzophenone in Feed for 2 Years

and G4, respectively). Dietary concentrations of 312, 625, and 1,250 ppm resulted in average daily doses of approximately 40, 80, and 160 mg benzophenone/kg body weight to males and 35, 70, and 150 mg/kg to females. No clinical findings were attributed to benzophenone exposure.

Pathology and Statistical Analyses

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

Liver: There was a positive trend in the incidences of hepatocellular adenoma in male mice; the incidences in the 625 and 1,250 ppm groups were significantly greater than that in the controls and exceeded the historical control range from feed studies (Tables 16, C3, and C4). Statistically significant increases in the incidences of multiple hepatocellular adenomas occurred in all exposed male mice. However, the incidences of carcinomas did not increase. Hepatoblastomas were also observed in exposed males. The incidences of hepatocellular adenoma in 625 and 1,250 ppm female mice increased, but the differences from the controls were not significant (Tables 16 and D3). The incidence of liver tumors in mice, primarily consisting of hepatocellular adenomas in NTP studies, has been found to be positively associated with body weight (Haseman *et al.*, 1997). When adjusted for the decreased body weight of exposed female mice, there were more hepatocellular adenomas in the 625 ppm and 1,250 ppm groups than expected (0 ppm: 6.8 expected, 5 observed; 312 ppm: 7.0 expected, 4 observed; 625 ppm: 6.2 expected, 10 observed; 1,250 ppm: 4.3 expected, 8 observed). Exposed males and females had increased incidences of eosinophilic foci, and males had increases in clear and mixed cell foci (Tables 16, C5, and D5). However, only the increase in clear cell foci in 1,250 ppm males was significant.

Microscopically, hepatocellular foci, hepatocellular adenomas, and hepatocellular carcinomas represent a continuum and, in this study, had the typical appearance of these lesions reported in B6C3F$_1$ mice. Eosinophilic and basophilic foci were small to moderately large lesions composed of hepatocytes with eosinophilic or basophilic cytoplasm that generally were somewhat enlarged. The hepatocytes were arranged in normal hepatic cords that merged with the surrounding normal hepatocytes. Foci had little or no compression of the surrounding normal hepatocytes, although some degree of compression was present in some larger foci. Adenomas were discrete masses with distinct borders that caused compression of the surrounding normal hepatic parenchyma. Adenomas usually were composed of hepatocytes that appeared similar to those seen in eosinophilic foci, except that in adenomas, the normal lobular architecture was not apparent, and plates of neoplastic hepatocytes intersected the surrounding normal hepatocytes at sharp angles rather than merging with them as in foci. Carcinomas were discrete masses that generally had irregular borders due to localized areas of growth of neoplastic hepatocytes into the surrounding normal parenchyma. The neoplastic hepatocytes often were somewhat atypical, but the major distinguishing features of carcinomas were the presence of abnormal patterns of growth. The most common abnormal growth pattern was formation of trabeculae of neoplastic hepatocytes that were three or more cell layers thick, while less commonly the neoplastic cells formed glandular structures or solid masses. Hepatoblastomas are malignant neoplasms that are presumed to be a primitive form of hepatocellular carcinoma. They were well-demarcated neoplastic masses independent of other hepatocellular tumors. The hepatoblastomas consisted of poorly differentiated, small, elongated, deeply basophilic cells with scant cytoplasm and hyperchromatic nuclei. The cells formed solid sheets, rosettes, and ribbons. They were often arranged around blood vessels. Some hepatoblastomas had large cystic spaces and necrotic areas. Three of the five mice had metastatic hepatoblastomas in the lungs.

Statistically significant increases in centrilobular hepatocyte hypertrophy were observed in all exposed groups of mice (Tables 16, C5, and D5). This hypertrophy was characterized by an increase in the size and staining intensity of the individual hepatocytes in centrilobular areas. These enlarged hepatocytes had a pale to brightly eosinophilic, finely granular cytoplasm. In males, the hypertrophied cells were admixed with numerous enlarged multinucleated hepatocytes having 5 to 20 hyperchromatic nuclei per cell. Most exposed males had multinucleated hepatocytes accompanied by

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Male				
Number Examined Microscopically	50	50	50	50
Clear Cell Focus[a]	2	7	7	12**
Eosinophilic Focus	5	8	11	10
Mixed Cell Focus	8	9	15	13
Hepatocyte, Centrilobular, Hypertrophy	0	44** (2.0)[b]	50** (2.0)	48** (3.0)
Hepatocyte, Multinucleated	0	41** (1.4)	47** (1.5)	48** (1.8)
Hepatocyte, Necrosis	1 (1.0)	6 (1.7)	8* (1.8)	8* (1.3)
Inflammation, Chronic Active	33 (1.0)	47** (1.1)	44** (1.2)	42* (1.1)
Hepatocyte, Degeneration, Cystic	0	0	5* (1.2)	30** (1.9)
Hepatocellular Adenoma, Multiple	2	8*	8*	12**
Hepatocellular Adenoma (includes multiple)[c]				
Overall rate[d]	11/50 (22%)	15/50 (30%)	23/50 (46%)	23/50 (46%)
Adjusted rate[e]	22.9%	31.5%	46.9%	46.6%
Terminal rate[f]	10/44 (23%)	14/44 (32%)	21/44 (48%)	21/45 (47%)
First incidence (days)	703	606	585	568
Poly-3 test[g]	P=0.006	P=0.239	P=0.010	P=0.011
Hepatocellular Carcinoma	8	5	6	6
Hepatoblastoma[h]				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.1%	2.1%	6.1%
Terminal rate	0/44 (0%)	1/44 (2%)	1/44 (2%)	2/45 (4%)
First incidence (days)	—[i]	730 (T)	730 (T)	606
Poly-3 test	P=0.057	P=0.497	P=0.502	P=0.123
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[j]				
Overall rate	18/50 (36%)	20/50 (40%)	25/50 (50%)	29/50 (58%)
Adjusted rate	37.0%	40.7%	50.9%	58.1%
Terminal rate	16/44 (36%)	16/44 (36%)	23/44 (52%)	25/45 (56%)
First incidence (days)	540	449	585	568
Poly-3 test	P=0.013	P=0.434	P=0.118	P=0.027

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Female				
Number Examined Microscopically	50	50	50	50
Clear Cell Focus	3	2	4	4
Eosinophilic Focus	2	2	7	7
Mixed Cell Focus	2	5	3	2
Hepatocyte, Centrilobular, Hypertrophy	0	29** (2.0)	44** (2.0)	37** (2.9)
Hepatocyte, Multinucleated	0	0	0	2 (1.0)
Hepatocyte, Necrosis	3 (2.0)	5 (2.0)	4 (1.5)	0
Inflammation, Chronic Active	44 (1.1)	40 (1.1)	41 (1.0)	36* (1.1)
Hepatocyte, Degeneration, Cystic	0	0	0	0
Hepatocellular Adenoma, Multiple	1	1	3	3
Hepatocellular Adenoma (includes multiple)[k]				
Overall rate	5/50 (10%)	4/50 (8%)	10/50 (20%)	8/50 (16%)
Adjusted rate	10.8%	8.5%	21.4%	18.1%
Terminal rate	5/40 (13%)	3/42 (7%)	10/41 (24%)	7/31 (23%)
First incidence (days)	729 (T)	680	729 (T)	435
Poly-3 test	P=0.109	P=0.494N	P=0.131	P=0.243
Hepatocellular Carcinoma	0	1	0	1
Hepatocellular Adenoma or Carcinoma[l]				
Overall rate	5/50 (10%)	5/50 (10%)	10/50 (20%)	9/50 (18%)
Adjusted rate	10.8%	10.7%	21.4%	20.3%
Terminal rate	5/40 (13%)	4/42 (10%)	10/41 (24%)	7/31 (23%)
First incidence (days)	729 (T)	680	729 (T)	435
Poly-3 test	P=0.081	P=0.624N	P=0.131	P=0.165

* Significantly different ($P \leq 0.05$) from the control group by the Poly-3 test
** $P \leq 0.01$
(T) Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year studies with feed controls given NTP-2000 diet (mean ± standard deviation): 90/460 (20.0% ± 7.1%), range 12%-30%
[d] Number of animals with neoplasm per number of animals with liver examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidences are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposed group is indicated by **N**.
[h] Historical incidence: feed 1/460 (0.2% ± 0.6%), range 0%-2%
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 145/460 (32.4% ± 9.1%), range 20%-47%
[k] Historical incidence: 40/457 (9.6% ± 2.4%), range 6%-12%
[l] Historical incidence: 53/457 (11.8% ± 3.1%), range 8%-16%

increases in the incidences of necrosis and chronic active inflammation. The 625 and 1,250 ppm male groups had significant increases in the incidences of cystic degeneration of hepatocytes. This lesion was characterized by multilocular cyst-like spaces within the hepatic parenchyma containing a pale, floccular, eosinophilic material. It is reported with a low incidence as a spontaneous finding in aged mice.

Histiocytic Sarcoma: In females, there was a positive trend in the incidences of histiocytic sarcoma (all organs); the incidence in 625 ppm females was significantly greater than that in the controls (Tables 17 and D3). Only two histiocytic sarcomas have been observed in historical feed study controls, and the incidence in the 625 ppm group exceeded the historical control range for all routes (Tables 17 and D4). In the current 2-year study, only females were affected, and the liver and lung were involved in all affected females. The histiocytic sarcomas were highly invasive in all three 1,250 ppm mice. Multiple organs throughout the body had neoplastic histiocytic lesions. Ovary, uterus, spleen, adrenal gland, kidney, urinary bladder, and multiple lymph nodes were affected in all three animals. Although multiple organs were involved in the five females of the 625 ppm group, fewer organs were affected. Histologically, cells that are characteristic of neoplastic histiocytes were large with relatively abundant, pale eosinophilic cytoplasm. Their nuclei were dark basophilic with round to oval shapes and inconspicuous nucleoli. Variation in the size and shape of some neoplastic cells and high cytoplasmic-to-nuclear ratios were observed. Occasional multinucleated giant cells were present (Plate 3). Fibrosis was scant. Growth was both infiltrative and expansive and extended on pleural and peritoneal surfaces. Metastatic neoplastic emboli were frequently present in blood vessels. Neoplastic histiocytic cells infiltrated the liver, expanded the hepatic sinusoids, and frequently formed nodular patterns or thick sheets that disrupted the hepatic parenchyma. In the lung, intravascular and perivascular infiltrates of neoplastic histiocytic cells were observed (Plate 4).

Kidney: Exposed female mice had significantly increased incidences of nephropathy accompanied by mineralization (Tables 18 and D5). The mineralization was characterized by basophilic mineral deposits in the cortical tubules and medullary collecting ducts. The severity of nephropathy was significantly increased in all exposed groups of male mice. Nephropathy was characterized by tubular degeneration, tubular regeneration, interstitial inflammation, dilatation of renal tubules, intratubular protein casts, and subcapsular regions of

TABLE 17
Incidences of Histiocytic Sarcoma in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Histiocytic Sarcoma[a]				
Overall rate[b]	0/50 (0%)	0/50 (0%)	5/50 (10%)	3/50 (6%)
Adjusted rate[c]	0.0%	0.0%	10.7%	6.9%
Terminal rate[d]	0/40 (0%)	0/42 (0%)	4/41 (10%)	2/31 (7%)
First incidence (days)	—[f]	—	718	651
Poly-3 test[e]	P=0.032	—[g]	P=0.031	P=0.108

[a] Historical incidence for 2-year studies with feed controls given NTP-2000 diet (mean ± standard deviation): 2/459 (0.3% ± 0.8%), range 0%-2%; all routes 18/1,258 (1.5% ± 2.2%), range 0%-8%
[b] Number of animals with neoplasm per number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence is the P value associated with the trend test. Beneath the exposed group incidences are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[f] Not applicable; no neoplasms in animal group
[g] Value of statistic cannot be computed

TABLE 18
Incidences of Selected Nonneoplastic Lesions in Mice in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm		625 ppm		1,250 ppm	
Male								
Kidney[a]	50		50		50		50	
Nephropathy[b]	49	(1.2)[c]	48	(1.4)▲	50	(1.7)▲	50	(3.0)▲
Cortex, Cyst	4		8		12*		22**	
Nose	50		50		50		50	
Olfactory Epithelium, Metaplasia	0		2	(1.0)	2	(1.0)	24**	(1.2)
Spleen	50		50		50		50	
Lymphoid Follicle, Hyperplasia, Lymphoid	17	(2.1)	31**	(2.5)	34**	(2.0)	32**	(2.2)
Testes	50		50		50		50	
Mineralization	0		1	(1.0)	4	(1.0)	12**	(1.1)
Female								
Kidney	50		50		50		50	
Nephropathy	21	(1.2)	33**	(1.1)	31*	(1.5)	30*	(1.7)▲
Mineralization	15	(1.0)	31**	(1.0)	36**	(1.1)	49**	(1.5)
Nose	50		50		50		50	
Olfactory Epithelium, Metaplasia	0		0		0		39**	(1.7)
Spleen	50		50		50		50	
Hematopoietic Cell Proliferation	16	(2.6)	35**	(2.1)	32**	(2.4)	27*	(2.8)
Lymphoid Follicle, Hyperplasia, Lymphoid	24	(2.5)	36**	(2.5)	37**	(2.7)	22	(2.9)

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

interstitial fibrosis scars. The nephropathy was accompanied by significantly increased incidences of cortex cysts in the 625 and 1,250 ppm groups.

Nose: The incidences of metaplasia of the olfactory epithelium were significantly increased in 1,250 ppm male and female groups (Tables 18, C5, and D5). The metaplasia was characterized by a replacement of normal olfactory epithelium by a single layer of ciliated columnar epithelium resembling normal respiratory epithelium. The metaplasia was focal to multifocal and involved the dorsal meatus, dorsal nasal septum, and ethmoid turbinates of levels II and III. Frequently, the metaplasia extended into underlying submucosal Bowman's glands.

Spleen: The incidences of hematopoietic cell proliferation in all exposed groups of female mice were significantly greater than that of the controls (Tables 18 and D5). Hematopoietic cell proliferation consisted of increased numbers of megakaryocytes and myeloid and erythroid precursors. Hyperplasia of lymphoid follicles was significantly increased in all exposed groups of males and in 312 and 625 ppm females (Tables 18, C5, and D5). Lymphoid follicular hyperplasia was characterized by white pulp lymphoid follicles enlarged from normal size to the point of follicular coalescence that is associated with malignant lymphoma.

Testes: The incidence of mineralization was significantly increased in 1,250 ppm males (Tables 18 and C5). The mineralization commonly occurred as basophilic deposits in the walls and lumen of small blood vessels and in the tunica. The mineralization was not associated with degeneration of the germinal epithelium.

TOXICOKINETIC STUDIES

Single-dose toxicokinetic studies were performed in male and female F344/N rats and $B6C3F_1$ mice (Appendix J). Plasma concentrations of the parent compound were determined following oral and intravenous administration of benzophenone. The plasma concentration of benzophenone versus time plots showed secondary maxima, apparently due to enterohepatic circulation. The data were analyzed by noncompartmental modeling and indicated no consistent sex-related or exposure-related effects in either species. In contrast, the plasma benzophenone concentrations taken during the 2-year study clearly showed a sex-related effect in rats. The area under the plasma concentration curve versus time plot was significantly higher for females at all but two exposure/AUC entries in Table J4. The dose based on food consumption (Tables G1 and G2), however, is similar for both sexes.

GENETIC TOXICOLOGY

Benzophenone showed no evidence of mutagenicity *in vitro* or *in vivo*. Benzophenone (1 to 1,000 µg/plate) did not induce mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver metabolic activation enzymes (Table E1; Mortelmans *et al*., 1986). Intraperitoneal injections of 200 to 500 mg benzophenone per kg body weight (three injections at 24 hour intervals) did not induce micronuclei in bone marrow polychromatic erythrocytes (PCEs) of male $B6C3F_1$ mice (Table E2). A small increase in the frequency of micronucleated PCEs was noted in the 400 mg/kg group, but the difference was not statistically significant. No increases in the frequencies of micronucleated normochromatic erythrocytes were seen in peripheral blood of male or female $B6C3F_1$ mice administered benzophenone for 14 weeks in feed over a concentration range of 1,250 to 20,000 ppm (Table E3). No significant alterations in the percentage of PCEs among total erythrocytes were noted in either micronucleus test, indicating no toxicity to the bone marrow from benzophenone treatment.

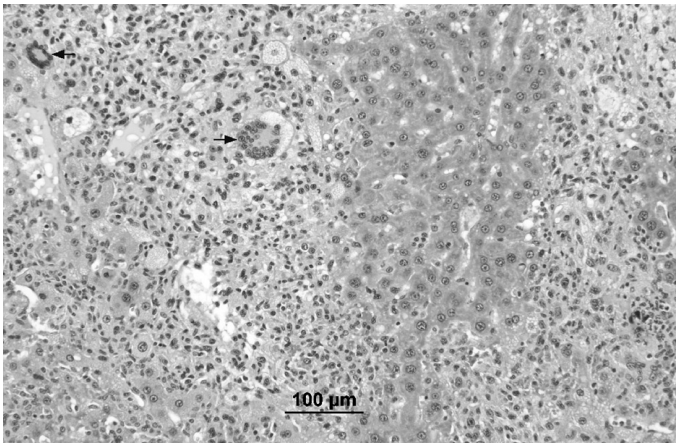


Plate 1
Histiocytic sarcoma in the liver of a female F344/N rat exposed to 625 ppm benzophenone in feed for 2 years. Note the hepatocytes surrounded by a massive infiltrate of neoplastic histiocytes with formation of multinucleated giant cells (arrows). H&E; 20×

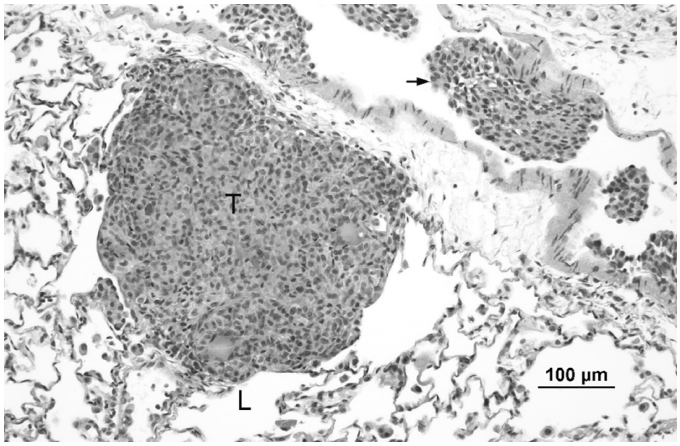


Plate 2
Metastatic histiocytic sarcoma (T) in the lung (L) of a female F344/N rat exposed to 625 ppm benzophenone in feed for 2 years. Note the multiple groups of intravascular neoplastic histiocytes (arrow). H&E; 20×

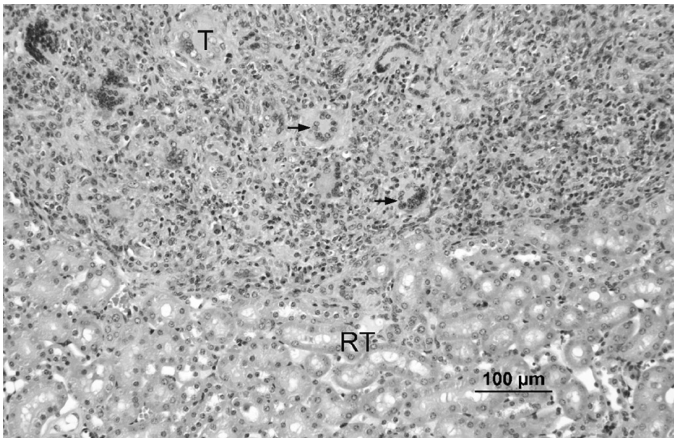


Plate 3
Histiocytic sarcoma (T) in the kidney of a female B6C3F$_1$ mouse exposed to 625 ppm benzophenone in feed for 2 years. Note the neoplastic histiocytes invading the adjacent renal tubule tissue (RT). Many multinucleated giant cells cells (arrows) are present. H&E; 20×

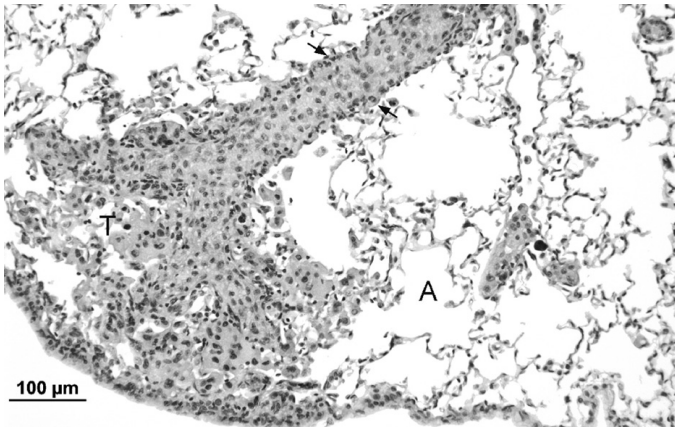


Plate 4
Metastatic histiocytic sarcoma (T) in the lung of a female B6C3F$_1$ mouse exposed to 1,250 ppm benzophenone in feed for 2 years. Note the intravascular neoplastic histiocytes (arrows) invading the adjacent alveoli (A). H&E; 20×

DISCUSSION AND CONCLUSIONS

Benzophenone is used to manufacture insecticides, agricultural chemicals, hypnotics, antihistamines, and other pharmaceuticals; as an ultraviolet curing agent in sunglasses and ink; as an additive in plastics, coatings, and adhesive formulations; and as a flavor ingredient. Concentrations of benzophenone in food products range from 0.57 ppm in nonalcoholic beverages to 3.27 ppm in frozen dairy products; it may also be an ingredient in baked goods, soft candy, gelatins, and puddings (NAS/NRC, 1979). Benzophenone was selected for toxicologic and carcinogenicity evaluations based on the potential for occupational and consumer exposure and the lack of chronic toxicity data. The National Toxicology Program previously performed 14-week toxicity studies on benzophenone and published the results in a separate report (NTP, 2000). The current 2-year studies were designed to evaluate and characterize the potential carcinogenicity of benzophenone in rats and mice. For the 2-year studies reported here, the highest exposure concentration selected was 1,250 ppm based on the 14-week studies that indicated this exposure level was minimally toxic across both species and sexes.

In the 14-week exposure to benzophenone at concentrations of 1,250, 2,500, 5,000, 10,000, or 20,000 ppm in rats and mice, the liver and kidney were identified as the primary target organs of benzophenone toxicity in rats (NTP, 2000). In mice, the liver was the major target of toxicity. In rats, liver changes were observed at exposure concentrations greater than or equal to 5,000 ppm, while in mice, microscopic changes in the liver were observed in all exposed groups. Gross (increased organ weights) and microscopic (hepatocellular hypertrophy) liver changes associated with benzophenone administration in males and females were accompanied by benzophenone-induced increases in the activity of pentoxyresorufin dealkylase, an enzyme activity linked to the cytochrome P450 2B isozyme. Liver hypertrophy (increases in cell size) is often attributed in part to induction of drug metabolizing enzymes. In rats, increased kidney weights were associated with a spectrum of renal changes in exposed male and female rats. One change found predominantly in 20,000 ppm animals, which died early, was papillary necrosis characterized by acute coagulative necrosis of the distal tips of the renal papillae. Unique lesions seen in rats were well-demarcated wedge-shaped areas of prominent tubule dilatation. In male rats, this change was present at exposure concentrations of 2,500 ppm and greater, while in females it occurred only at 10,000 and 20,000 ppm. Foci of tubule regeneration were increased in incidence and/or severity relative to the controls in exposed males and females.

In the current 2-year studies, there were no differences in survival of female rats or male mice exposed to benzophenone compared to controls. Survival was significantly reduced in 1,250 ppm male rats, most likely due to nephropathy. Female mice exposed to 1,250 ppm benzophenone tended to have decreased survival toward the end of the study, but the difference from the control group was not statistically significant.

The target organs of toxicity in the 2-year studies were liver, kidney, nose, and testes. Neoplastic responses occurred in the kidney, liver, and hematopoietic system.

In the 2-year rat study, exposed animals exhibited a positive trend in the incidences of renal tubule adenoma. The NTP has found that examination of the entire kidney, by step sectioning of residual tissues, enables a more precise evaluation of the potential chemical-related induction of renal proliferative lesions than observations made from single sections, particularly when the proliferative lesions are small and identified only by microscopic examination (Eustis *et al.*, 1994). For benzophenone, this extended evaluation of the male rat kidney showed significant increases in the incidences of renal tubule adenoma in 625 and 1,250 ppm males and increased incidences of hyperplasia in all exposed groups of males. Incidences of renal tubule hyperplasia in all exposed female groups were significantly greater than that of the control group when the single and step section evaluations were combined.

Within the NTP 2-year carcinogenicity studies, the kidney is the second most commonly affected site in male

rats for chemically associated site-specific neoplasms (NTP, 2004b). In the majority of the studies, the increases are primarily of adenomas, and in many instances there is a concurrent dose-related increase in the severity of chronic progressive nephropathy. Chronic nephropathy may influence the induction, development, or progression of renal neoplasms in several ways, including a reduction in target cell population and/or increased number of cells in the replicative cycle due to chronic inflammation and continued degeneration and necrosis, alterations in vascularity as a result of fibrosis, or other alterations in microenvironment. The pathogenesis of chemically induced renal tubule neoplasms has not been determined; however it appears to be complex with genotoxic and nongenotoxic modes (Barrett and Huff, 1991; Short, 1993; Hard, 1998). Data from retrospective reviews of NTP 2-year carcinogenesis studies suggest that an increased severity of nephropathy may contribute to overall tumor response (Seely *et al.*, 2002). However, any contribution appears to be marginal, and additional factors are likely involved.

In female rats, the incidence of mononuclear cell leukemia was marginally increased in the 625 ppm group. Male rats exposed to 312 or 625 ppm benzophenone exhibited significantly increased incidences of mononuclear cell leukemia. Significantly increased incidences were not observed in females exposed to 1,250 ppm, and the incidence in males exposed to 1,250 ppm was similar to the incidence in control males. Mononuclear cell leukemia is generally a late developing neoplasm with most observed in animals after 18 months on study. The incidence of mononuclear cell leukemia in males exposed to 1,250 ppm may have been somewhat higher had survival not been reduced in the last quarter of the study. The incidences of mononuclear cell leukemia in 312 and 625 ppm males and all exposed groups of females were outside the historical control ranges of 30% to 68% in male controls from 2-year NTP feed studies and 12% to 38% in control females; however, the incidence in the female control group was also outside the historical range. The data from this study of benzophenone were included in the historical control dataset, and the 38% incidence was the highest in the dataset. There is no obvious explanation for the higher incidence in the control group.

Mononuclear cell leukemia, a common neoplasm in F344/N rats, is generally thought to arise within the spleen. The spleen is the first and most commonly affected organ, followed by involvement of the liver. With progression, mononuclear cell leukemia becomes widespread and involves multiple organs. Earlier onset and wider distribution of mononuclear cell leukemia in exposed groups would indicate that the increased incidences of mononuclear cell leukemia were treatment related; however, there was no evidence that mononuclear cell leukemia occurred earlier in exposed groups than in control groups in this study. Assessment of the distribution of mononuclear cell leukemia in exposed and control males and females (Table 11) demonstrated lesser involvement of the spleen and liver in the 625 and 1,250 ppm male groups and greater involvement of the spleen and liver in the 625 and 1,250 ppm female groups when compared to the control groups. Although a hint of increased grade 3 mononuclear cell leukemia was observed in exposed females, there was no significant increase in the average severity grade in exposed versus control groups. The average severity grade was significantly decreased in males. Even though the incidences in exposed groups often exceeded the historical control ranges, because the incidences in the 1,250 ppm groups were not significantly increased and there was no evidence of early occurrence or wider distribution in exposed groups, the increased incidences were only considered equivocal evidence of carcinogenicity.

Benzophenone exposure resulted in a positive trend in the incidence of histiocytic sarcoma in female mice, and one 625 ppm and two 1,250 ppm female rats had histiocytic sarcomas. This neoplasm is rare; none have been observed in historical feed study control rats, and only two have been observed in feed study control mice given the NTP-2000 diet. In historical controls from all routes of exposure, histiocytic sarcoma was observed in one of 1,209 (0.08%) historical control rats and 18 of 1,258 historical control mice (1.4%). Histiocytic sarcomas are classified as hematopoietic tumors of the mononuclear phagocyte system based upon the morphology of the neoplastic cells and the presence of lysozyme, Mac-2, and mononuclear phagocyte antigens. The specific origin of the neoplastic histiocytic cells is undetermined. One or more cell populations may be involved. Bone marrow cells, tissue histiocytes, Kupffer's cells in the liver, and circulating macrophages have been suggested. Histiocytic sarcomas are slightly more common in female than male mice and in mice than rats (Frith *et al.*, 1993). Although the spontaneous incidence of this tumor is low in both mice and rats, the frequency varies widely among different strains of mice and rats. Histiocytic sarcomas are more common in Sprague-Dawley rats, with an overall incidence of 4.7%, than in the Fischer 344, used by the NTP, and Osborne-Mendel

strains. In mice exposed to benzophenone, the liver and lung were involved in all affected animals. In the 1,250 ppm female mice, the histiocytic sarcomas were highly invasive. Multiple organs throughout the body had neoplastic histiocytic lesions. All affected rats exposed to benzophenone had lung lesions. Only one rat in the 625 ppm group had organs affected throughout the body. Chemical-associated increases in the incidences of histiocytic sarcomas have not been seen in rats in NTP studies and are uncommon in mice. Increased incidences in mice occurred in studies of 1,3-butadiene (NTP, 1993), tetrafluoroethylene (NTP, 1996a), and phenolphthalein (NTP, 1996b). The increased incidences in the 625 and 1,250 ppm female groups and the increased invasiveness in the 1,250 ppm mice were considered related to benzophenone exposure and some evidence of carcinogenicity. The low incidence of this rare neoplasm in female rats was considered equivocal evidence of carcinogenic activity.

Female mice in all exposed groups had increased incidences of spleen hematopoietic cell proliferation. The proportions of these cells varied from animal to animal. Hematopoietic cell proliferation, also termed extramedullary hematopoiesis, is a common and normal phenomenon in the spleen of mice, to a greater degree in females than males. The incidence in the control female group in this study is consistent with previous NTP studies (Ward *et al.*, 1999). Increased hematopoietic cell proliferation has been associated with anemia and chronic inflammatory lesions. Evidence of an anemia with minimal severity was observed in rats and mice during the 14-week studies at higher doses than were used in the 2-year study (NTP, 2000).

Increases in the incidences of hepatocellular adenoma were observed in male and female mice. Hepatoblastomas were also observed in exposed males; however, the increased incidence was not statistically significant. Female mice showed more hepatocellular adenomas than expected in the 625 and 1,250 ppm groups when corrected for decreased body weight (0 ppm: 6.8 expected, 5 observed; 312 ppm: 7.0 expected, 4 observed; 625 ppm: 6.2 expected, 10 observed; 1,250 ppm: 4.3 expected, 8 observed) (Haseman *et al.*, 1997). Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a biological and morphological continuum in progression of proliferative lesions. Because the malignant potential of hepatoblastomas and hepatocellular carcinomas appears similar and hepatoblastomas are often observed within hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastoma with those of adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. The combined incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma was significantly increased in 1,250 ppm males, and the incidences showed a positive trend. This was considered some evidence of carcinogenicity. The response in females was considered equivocal.

Benzophenone exposure significantly increased incidences of hepatocellular centrilobular hypertrophy in male and female rats and mice. The description of the centrilobular hypertrophy was in agreement with previous reports which also describe clumping of basophilic material in centrilobular hepatocytes (Burdock *et al.*, 1991). The hepatocellular enlargement observed in the current 2-year studies was probably accompanied by induction of cytochromes P450 as observed in the 14-week studies (NTP, 2000). The pattern of induction described in the 14-week studies was similar to that associated with exposure to phenobarbital, in that pentoxyresorufin dealkylase activity, and not that of ethoxyresorufin deethylase, was induced.

In the current study, the incidences of metaplasia of the olfactory epithelium were significantly increased in the 1,250 ppm male and female mice. This was a species-specific effect, as rats did not display similar lesions, possibly because of differences in the anatomy of the rat nasal cavity and potential lower relative exposures to benzophenone in rats. The metaplasia was focal to multifocal, primarily involved the dorsal meatus, dorsal nasal septum, and ethmoid turbinates, and was characterized by a replacement of normal olfactory epithelium by a single layer of ciliated columnar epithelium resembling normal respiratory epithelium. This metaplasia is considered the result of repair following earlier damage to the more sensitive olfactory epithelium. The submucosal (Bowman's) glands were also involved. The mechanism by which benzophenone caused this lesion is unknown; however, enzymatic metabolism of benzophenone in the olfactory epithelium, which has a high concentration of cytochrome P450, may be involved. Some compounds, such as phosphodiesterase inhibitors, that require metabolic activation by the cytochrome P450 enzyme system have been shown to cause olfactory epithelial injury, chronic hyperplastic/regenerative lesions, and olfactory neoplasms following oral or inhalation exposure in rodents (Pino *et al.*, 1999).

All exposed groups of male and female rats in the current studies displayed significantly decreased incidences of thyroid gland C-cell hyperplasia. The C-cells synthesize, store, and release the hormone calcitonin in response to physiologic alterations in serum calcium levels. As F344 rats age, there is a diffuse increase in C-cells. Thyroid gland C-cell hyperplasia is a common age-associated change in male and female rats in chronic NTP studies (Boorman *et al.*, 1996). Incidences of C-cell hyperplasia in control groups of both sexes are within expected values. The decreased incidences of thyroid gland C-cell hyperplasia were not related to the severity of nephropathy in males and appear to be treatment related. The possible relationship of calcium regulation by C-cells to benzophenone exposure is unknown.

Decreases in the incidences and multiplicities of mammary gland fibroadenoma were observed in female rats exposed to benzophenone. Fibroadenomas are the most common neoplasm of the mammary gland in female rats, occurring in 213/460 (46%, range 28% to 55%) NTP feed study control animals. The incidence of mammary gland tumors in NTP studies has been found to be positively associated with body weight. However, the decreased incidence of mammary gland tumors in this study could not be attributed to decreased body weights of exposed females, as the 1,250 ppm females had significantly lower incidences of this neoplasm after correcting for decreased body weight (Haseman *et al.*, 1997). Interestingly, benzophenone-based derivatives have shown impressive inhibitory activity of steroid sulfatase, an enzyme that regulates the formation of estrone and subsequent conversion to estradiol, and may be developed for therapeutic use in the treatment of hormone-dependent breast cancer (Hejaz *et al.*, 2004).

Plots of plasma concentration of benzophenone versus time in the single-dose toxicokinetic studies showed evidence of enterohepatic circulation. The Phase II metabolism of benzophenone has not been well characterized. Benzhydrol has been determined to be a metabolite (Nakagawa *et al.*, 2000). The metabolite participating in the recirculation is proposed to be the glucuronide of benzhydrol (Appendix J). This metabolite may be the labile glucuronide described earlier (Robinson, 1958; Robinson and Williams, 1957).

The higher plasma concentrations of benzophenone in female rats compared to males may depend on the sex-related differences in organic anion transporters (OAT) in the kidney (Buist and Klaassen, 2004). When the rate of elimination of parent or a metabolite is determined by the rate of renal clearance, elimination has been shown to be slower in female rats (Griffin *et al.*, 1997; Dill *et al.*, 1998). It is likely that benzhydrol glucuronide is a major urinary metabolite and is an OAT substrate. The enterohepatic circulation of this metabolite may mask the differences in renal clearance after a single dose, but as this process reaches "equilibrium," the difference in renal clearance becomes apparent.

Benzophenone showed no evidence of genotoxicity *in vitro* or *in vivo* in standard mutagenicity assays. Benzophenone was negative in *Salmonella typhimurium* gene mutation assays, with or without exogenous metabolic activation enzymes (Mortelmans *et al.*, 1986; Takemoto *et al.*, 2002), and no increases in micronucleated erythrocytes were noted in mice after acute or subchronic exposure to benzophenone. Interestingly, use of human recombinant P450 enzyme preparations, including P450 family 1 enzymes, in a *S. typhimurium umu* gene expression assay with benzophenone and two metabolites, benzhydrol and *p*-benzoylphenol, produced dose-related increases in gene expression (Takemoto *et al.*, 2002). This observation is intriguing because P450 1B1 is constitutively expressed in human skin cells, and benzophenone is an ingredient in some topical sunscreen preparations.

CONCLUSIONS

Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity** of benzophenone in male F344/N rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344/N rats may have been related to benzophenone exposure. There was *equivocal evidence of carcinogenic activity* of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma. There was *some evidence of carcinogenic activity* of benzophenone in male $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was *some evidence of carcinogenic activity* of benzophenone in female $B6C3F_1$ mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female $B6C3F_1$ mice may have been related to benzophenone exposure.

Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats

and in the liver, kidney, nose, and spleen of male and female mice.

Decreased incidences of mammary gland fibroadenoma in female rats were related to benzophenone exposure.

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

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF BENZOPHENONE

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	25	12	16	44
Natural deaths	3	11	3	4
Survivors				
Terminal sacrifice	22	27	31	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, colon	(50)	(50)	(50)	(50)
Intestine large, rectum	(50)	(50)	(50)	(50)
Leiomyoma			1 (2%)	
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Intestine small, ileum	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma	2 (4%)		1 (2%)	
Mesentery	(9)	(12)	(8)	(4)
Oral mucosa	(8)	(8)	(5)	(7)
Gingival, squamous cell papilloma		1 (13%)		
Pharyngeal, squamous cell papilloma				1 (14%)
Pancreas	(50)	(50)	(50)	(50)
Mixed tumor benign	1 (2%)			
Salivary glands	(49)	(50)	(50)	(49)
Schwannoma malignant	1 (2%)			
Stomach, forestomach	(50)	(49)	(49)	(50)
Stomach, glandular	(50)	(50)	(49)	(50)
Tongue	(1)	(1)		(1)
Squamous cell papilloma	1 (100%)	1 (100%)		1 (100%)
Tooth	(3)	(5)	(2)	(3)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Chordoma, metastatic, bone	1 (2%)			
Schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma		1 (2%)		
Adrenal medulla	(50)	(49)	(50)	(50)
Pheochromocytoma malignant			2 (4%)	1 (2%)
Pheochromocytoma benign	8 (16%)	5 (10%)	6 (12%)	3 (6%)
Bilateral, pheochromocytoma benign			2 (4%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Parathyroid gland	(49)	(45)	(48)	(49)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	10 (20%)	6 (12%)	12 (24%)	5 (10%)
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma			3 (6%)	
C-cell, adenoma	10 (20%)	6 (12%)	6 (12%)	4 (8%)
C-cell, carcinoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Follicular cell, adenoma	2 (4%)	2 (4%)	3 (6%)	3 (6%)
General Body System				
Peritoneum	(1)		(1)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma		3 (6%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(49)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	43 (86%)	41 (82%)	40 (80%)	42 (84%)
Interstitial cell, adenoma	2 (4%)	5 (10%)	6 (12%)	6 (12%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Lymph node	(19)	(20)	(16)	(19)
Lymph node, mandibular	(5)	(1)	(2)	
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Chordoma, metastatic, bone	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Thymus	(48)	(48)	(48)	(48)
Chordoma, metastatic, bone	1 (2%)			
Integumentary System				
Mammary gland	(50)	(48)	(50)	(50)
Fibroadenoma	2 (4%)	2 (4%)		1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		3 (6%)	1 (2%)	
Fibrous histiocytoma	1 (2%)			
Keratoacanthoma	10 (20%)	3 (6%)	3 (6%)	3 (6%)
Osteosarcoma	1 (2%)	2 (4%)		
Schwannoma malignant				1 (2%)
Squamous cell papilloma	1 (2%)	2 (4%)		
Trichoepithelioma			1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	3 (6%)	3 (6%)	2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Chordoma	1 (2%)			
Osteosarcoma			1 (2%)	
Skeletal muscle	(2)	(2)	(1)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	1 (2%)		
Alveolar/bronchiolar carcinoma			1 (2%)	2 (4%)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Chordoma, metastatic, bone	1 (2%)			
Osteosarcoma, metastatic, skin		2 (4%)		
Pheochromocytoma malignant, metastatic, adrenal medulla			2 (4%)	1 (2%)
Mediastinum, myxosarcoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(50)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Pelvis, transitional epithelium, carcinoma				1 (2%)
Renal tubule, adenoma	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	27 (54%)	41 (82%)	39 (78%)	24 (48%)
Mesothelioma malignant	2 (4%)	3 (6%)	2 (4%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	50
Total primary neoplasms	139	139	143	109
Total animals with benign neoplasms	49	47	49	50
Total benign neoplasms	103	86	92	77
Total animals with malignant neoplasms	33	42	40	26
Total malignant neoplasms	36	53	51	32
Total animals with metastatic neoplasms	2	5	4	1
Total metastatic neoplasms	9	12	6	1

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 2 5	4 9 5	5 0 6	5 4 9	5 5 3	5 5 2	5 8 4	6 3 2	6 3 4	6 3 8	6 4 5	6 6 2	6 6 6	6 7 6	6 7 6	6 8 0	6 8 0	6 8 1	6 9 0	6 9 3	6 9 4	7 0 4	7 0 4	7 0 9	7 0 9
Carcass ID Number	0 2 6	0 2 3	0 1 7	0 1 4	0 1 9	0 3 3	0 3 7	0 0 8	0 4 4	0 2 1	0 1 2	0 3 9	0 3 2	0 3 0	0 5 0	0 0 9	0 2 8	0 4 5	0 4 9	0 3 5	0 2 5	0 2 2	0 2 9	0 1 3	0 2 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X											
Mesentery		+		+																			+		
Mesothelioma malignant, metastatic, epididymis				X																					
Oral mucosa									+			+			+				+			+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis				X																					
Mixed tumor benign																									
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth										+				+											
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, bone						X																			
Schwannoma malignant																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X				X	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X						X				X			X	X	X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X								X	X				X		X
C-cell, carcinoma																									
Follicular cell, adenoma									X																

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 1 5	7 2 5	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 7	0 2 0	0 0 3	0 0 1	0 0 2	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 7	0 3 1	0 3 4	0 3 6	0 3 8	0 4 0	0 4 1	0 4 2	0 4 3	0 4 8	0 0 4	0 0 5	0 0 6	0 1 1	0 1 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																								X		2
Mesentery		+							+						+		+			+	+					9
Mesothelioma malignant, metastatic, epididymis																										1
Oral mucosa	+															+										8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis																										1
Mixed tumor benign									X																	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																							X			1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue											+															1
Squamous cell papilloma											X															1
Tooth											+															3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, bone																										1
Schwannoma malignant									X																	1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X				X													X				X	X	8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X																	X								10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma										X		X					X	X		X						10
C-cell, carcinoma							X																			1
Follicular cell, adenoma																				X						2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 2 5	4 9 5	5 0 6	5 4 9	5 5 3	5 8 2	5 8 4	6 3 2	6 3 4	6 3 8	6 4 5	6 6 2	6 6 6	6 7 6	6 7 6	6 8 0	6 8 0	6 8 1	6 9 0	6 9 3	6 9 4	7 0 4	7 0 4	7 0 9	7 0 9
Carcass ID Number	0 2 6	0 2 3	0 1 7	0 1 4	0 1 9	0 3 3	0 3 7	0 0 8	0 4 4	0 2 1	0 1 2	0 3 9	0 3 2	0 3 0	0 5 0	0 0 9	0 2 8	0 4 5	0 4 9	0 3 5	0 2 5	0 2 2	0 2 9	0 1 3	0 2 4
General Body System																									
Peritoneum				+																					
Mesothelioma malignant, metastatic, epididymis				X																					
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis				X																					
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis				X																					
Bilateral, interstitial cell, adenoma				X	X	X		X	X	X	X	X	X	X	X	X		X	X	X		X	X		X
Interstitial cell, adenoma		X	X																						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+		+		+	+	+	+		+	+	+		+	+		+		+		
Lymph node, mandibular	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, bone						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma, metastatic, bone						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																									
Keratoacanthoma							X									X					X	X			
Osteosarcoma																									
Squamous cell papilloma																								X	
Subcutaneous tissue, fibroma																X					X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma						X																			
Skeletal muscle	+	+																							

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 1 5	7 2 5	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 7	0 2 0	0 0 3	0 0 1	0 0 2	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 7	0 3 1	0 3 4	0 3 6	0 3 8	0 4 0	0 4 1	0 4 2	0 4 3	0 4 8	0 4 4	0 4 5	0 4 6	0 1 1	0 1 6	Total Tissues/ Tumors
General Body System																										
Peritoneum																										1
Mesothelioma malignant, metastatic, epididymis																										1
Genital System																										
Coagulating gland																		+								1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X			1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis																										1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	43
Interstitial cell, adenoma																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+			+																		+	+	19
Lymph node, mandibular	+	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma, metastatic, bone																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Chordoma, metastatic, bone																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma					X																					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma		X																								1
Keratoacanthoma	X	X			X								X	X				X								10
Osteosarcoma								X																		1
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma							X												X					X		5
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma																										1
Skeletal muscle																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 2 5	4 9 5	5 0 6	5 4 9	5 5 3	5 8 2	5 8 4	6 3 2	6 3 4	6 3 8	6 4 5	6 6 2	6 6 6	6 7 6	6 7 6	6 8 0	6 8 0	6 8 1	6 9 0	6 9 3	6 9 4	7 0 4	7 0 4	7 0 9	7 0 9
Carcass ID Number	0 2 6	0 2 3	0 1 7	0 1 4	0 1 9	0 3 3	0 3 7	0 0 8	0 4 4	0 2 1	0 1 2	0 3 9	0 3 2	0 3 0	0 5 0	0 0 9	0 2 8	0 4 5	0 4 9	0 3 5	0 2 5	0 2 2	0 2 9	0 1 3	0 2 4
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																								+	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X						
Chordoma, metastatic, bone						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X		X		X	X	X	X	X	X		X	X	X	X	X	X		X		X	X	
Mesothelioma malignant				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 1 5	7 2 5	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 4 7	0 2 0	0 0 3	0 0 1	0 0 2	0 0 7	0 1 0	0 1 5	0 1 6	0 1 8	0 2 7	0 3 1	0 3 4	0 3 6	0 3 8	0 4 0	0 4 1	0 4 2	0 4 3	0 4 8	0 4 4	0 0 5	0 0 6	0 1 1	0 1 6	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X													X	4
Chordoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X					X					X	X				X				X		X		27
Mesothelioma malignant																								X		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	344	373	484	499	526	535	543	590	609	610	624	641	653	657	673	698	698	702	704	709	710	715	715	729	729
Carcass ID Number	096	054	085	061	069	066	070	079	072	053	091	088	100	095	086	064	067	099	075	097	093	052	059	051	057
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+			+			+			+											
Mesothelioma malignant, metastatic, epididymis								X																	
Oral mucosa					+												+								
Gingival, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis																									
Tongue																									
Squamous cell papilloma																									
Tooth	+				+						+			+	+										
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign															X		X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X										X	X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X		
C-cell, carcinoma																									
Follicular cell, adenoma																				X		X			
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 6 0	0 6 5	0 6 8	0 7 3	0 7 6	0 7 7	0 7 8	0 8 0	0 8 1	0 8 2	0 8 3	0 8 7	0 8 9	0 9 0	0 9 4	0 9 8	0 5 5	0 5 6	0 5 8	0 6 2	0 6 3	0 7 1	0 7 4	0 8 4	0 9 2	Total Tissues/ Tumors
Genital System																										
Coagulating gland																								+		1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X				X					3
Carcinoma												X							X							3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis				X																						1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis				X																						2
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Interstitial cell, adenoma			X						X	X																5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node			+		+												+		+							20
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Fibroadenoma														X												2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma					X													X								3
Keratoacanthoma																										3
Osteosarcoma													X													2
Squamous cell papilloma			X	X																						2
Subcutaneous tissue, fibroma																										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	3 4 4	3 7 3	4 8 4	4 9 9	5 2 6	5 3 5	5 4 3	5 9 0	6 0 9	6 1 0	6 2 4	6 4 1	6 5 3	6 5 7	6 7 3	6 9 8	6 9 8	7 0 2	7 0 4	7 0 9	7 1 0	7 1 5	7 1 5	7 2 9
Carcass ID Number	0 9 6	0 5 4	0 8 5	0 6 1	0 6 9	0 6 6	0 7 0	0 7 9	0 7 2	0 5 3	0 9 1	0 8 8	1 0 0	0 9 5	0 8 6	0 6 4	0 6 7	0 9 9	0 7 5	0 9 7	0 9 3	0 5 2	0 5 9	0 5 1	0 5 7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Carcinoma, metastatic, thyroid gland																									
Carcinoma, metastatic, adrenal cortex																									
Osteosarcoma, metastatic, skin																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									X
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X		X
Mesothelioma malignant								X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 6 0	0 6 5	0 6 8	0 7 3	0 7 6	0 7 7	0 7 8	0 8 0	0 8 1	0 8 2	0 8 3	0 8 7	0 8 9	0 9 0	0 9 4	0 9 8	0 5 5	0 5 6	0 5 8	0 6 2	0 6 3	0 7 1	0 7 4	0 8 4	0 9 2	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, thyroid gland				X																						1
Carcinoma, metastatic, adrenal cortex														X												1
Osteosarcoma, metastatic, skin													X													2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Renal tubule, carcinoma															X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X			41
Mesothelioma malignant				X							X															3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

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

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	117	120	121	125	127	131	132	136	137	147	148	149	102	106	107	112	123	128	130	133	139	142	143	144	145	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																				X						1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma	X																									1
Hepatocellular adenoma																						X				1
Mesentery										+		+							+			+				8
Oral mucosa				+		+										+										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant	X								X																	2
Pheochromocytoma benign				X								X		X							X					6
Bilateral, pheochromocytoma benign						X																				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X			X										X								X	12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma			X									X														3
C-cell, adenoma										X						X										6
C-cell, carcinoma												X								X						2
Follicular cell, adenoma														X												3
General Body System																										
Peritoneum																										1
Mesothelioma malignant, metastatic, epididymis																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	4 8 6	4 9 4	4 9 9	5 4 3	5 4 3	5 9 0	6 1 3	6 2 4	6 6 9	6 8 7	6 9 0	6 9 1	7 0 5	7 0 8	7 0 8	7 0 8	7 0 8	7 1 1	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 4 1	1 2 2	1 2 6	1 0 8	1 4 0	1 1 6	1 3 5	1 2 9	1 0 1	1 0 4	1 5 0	1 0 3	1 1 1	1 1 9	1 2 4	1 3 4	1 3 8	1 4 6	1 1 8	1 0 5	1 0 9	1 1 0	1 1 3	1 1 4	1 1 5
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma				X			X																		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, epididymis								X					X												
Bilateral, interstitial cell, adenoma				X	X		X		X	X	X	X			X	X	X		X	X	X	X	X	X	
Interstitial cell, adenoma	X					X								X				X							X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+	+	+				+			+	+	+		+							
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																						X			
Keratoacanthoma									X																
Trichoepithelioma																									
Subcutaneous tissue, fibroma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle						+																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma										X															
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	11217	11220	11221	11225	11227	11231	11232	11236	11237	11247	11248	11249	11402	11406	11407	11412	11423	11428	11430	11433	11439	11442	11443	11444	11445	Total Tissues/ Tumors
Genital System																												
Coagulating gland												+																1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X										1
Carcinoma																												3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, epididymis																												2
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma						X																						6
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+	+		+					+	+			+		+									+	16
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant, metastatic, adrenal medulla									X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																												1
Keratoacanthoma			X										X															3
Trichoepithelioma							X																					1
Subcutaneous tissue, fibroma																									X	X		3
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma		X																										1
Skeletal muscle																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																												1
Pheochromocytoma malignant, metastatic, adrenal medulla	X								X																			2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	4 8 6	4 9 4	4 9 9	5 4 3	5 4 3	5 9 0	6 1 3	6 2 4	6 6 9	6 8 7	6 9 0	6 9 1	7 0 5	7 0 8	7 0 8	7 0 8	7 0 8	7 1 1	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	1 4 1	1 2 2	1 2 6	1 0 8	1 4 0	1 1 6	1 3 5	1 2 9	1 0 1	1 0 4	1 5 0	1 0 3	1 1 1	1 1 9	1 2 4	1 3 4	1 3 8	1 4 6	1 1 8	1 0 5	1 0 9	1 1 0	1 1 3	1 1 4	1 1 5
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland								+											+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X			X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Mesothelioma malignant								X					X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 1 7	1 2 0	1 2 1	1 2 5	1 2 7	1 3 1	1 3 2	1 3 6	1 3 7	1 4 7	1 4 8	1 4 9	1 0 2	1 0 6	1 0 7	1 1 2	1 2 3	1 2 8	1 3 0	1 3 3	1 3 9	1 4 2	1 4 3	1 4 4	1 4 5	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																				X						2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X		X	39
Mesothelioma malignant																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	632	634	634	634	635	637	639	641	641	653	662	669	675	680	688	691	694	708	708	708	708	708	726	729	729	
Carcass ID Number	17 1	16 3	17 2	19 4	15 9	16 4	17 7	16 7	19 9	17 8	19 6	19 5	18 6	18 7	17 0	15 1	15 4	15 7	16 5	18 4	18 5	19 3	18 3	16 9	17 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+											+	+			+							4
Oral mucosa											+				+		+									7
Pharyngeal, squamous cell papilloma											X															1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Tooth																+								+		3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign											X											X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X																		X					5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X						X								4
C-cell, carcinoma																				X						1
Follicular cell, adenoma																										3
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 8 8 0 2 2 2 3 3 4 4 5 6 6 8 9 9 0 0 0 1 1 2 2 2 7 8 7 9 9 9 7 7 0 9 5 9 9 2 3 3 1 4 4 3 7 1 1 4 4
Carcass ID Number	1 1 1 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 9 5 7 6 6 8 6 6 0 5 8 6 9 8 5 8 2 0 1 5 1 2 3 6 4 0 7 5 3 0 7 8 6 8 0 2 1 2 8 9 8 2 0 1 5 1 2 3 6 4 0
Genital System	
Epididymis	+ +
Preputial gland	+ M
Adenoma	
Carcinoma	X
Prostate	+ +
Seminal vesicle	+ + + + + + + + + M + + + + + + + + + + + + + + +
Testes	+ +
Bilateral, interstitial cell, adenoma	X X X X X X X X X X X X X X X X X X X X X X X X X
Interstitial cell, adenoma	X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, mandibular	M M M M M M M M M M M M M M M M M M M M M M M M M
Lymph node, mesenteric	+ +
Spleen	+ +
Thymus	+ +
Integumentary System	
Mammary gland	+ +
Fibroadenoma	X
Skin	+ +
Keratoacanthoma	X
Schwannoma malignant	X
Subcutaneous tissue, fibroma	X X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar carcinoma	
Pheochromocytoma malignant, metastatic, adrenal medulla	X
Mediastinum, myxosarcoma	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+ +
Harderian gland	+ +

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	6 3 2	6 3 4	6 3 4	6 3 4	6 3 5	6 3 7	6 3 9	6 4 1	6 4 1	6 5 3	6 6 2	6 6 9	6 7 5	6 8 0	6 8 1	6 9 1	6 9 4	7 0 8	7 0 8	7 0 8	7 0 8	7 0 8	7 2 6	7 2 9	7 2 9	
Carcass ID Number	1 7 1	1 6 3	1 7 2	1 9 4	1 5 9	1 6 4	1 7 7	1 6 7	1 9 9	1 7 8	1 9 6	1 9 5	1 8 6	1 8 7	1 7 0	1 5 1	1 5 4	1 5 7	1 6 5	1 8 4	1 8 5	1 9 3	1 8 3	1 6 9	1 7 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																							X			1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X		X	42
Interstitial cell, adenoma			X										X							X				X		6
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+		+	+		+				+								+			+	+			19
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma									X									X								3
Schwannoma malignant																										1
Subcutaneous tissue, fibroma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma						X																X				2
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Mediastinum, myxosarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 6 6 6 8 8 0 2 2 2 3 3 4 4 5 6 6 8 9 9 0 0 0 1 1 2 2 2 2 7 8 7 9 9 9 7 7 0 9 5 9 9 2 3 3 1 4 4 3 7 1 1 4 4
Carcass ID Number	1 1 1 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 9 5 7 6 7 8 6 6 0 5 8 6 9 8 5 8 9 6 7 9 9 5 5 7 8 7 5 3 0 6 8 6 8 0 2 1 2 8 9 8 2 0 1 5 1 2 3 6 4 0
Urinary System	
Kidney	+ +
Pelvis, transitional epithelium, carcinoma	X
Renal tubule, adenoma	X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X X X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	6 3 2	6 3 4	6 3 4	6 3 4	6 3 5	6 3 7	6 3 9	6 4 1	6 4 1	6 5 3	6 6 2	6 6 9	6 7 5	6 8 0	6 8 1	6 9 1	6 9 4	7 0 8	7 0 8	7 0 8	7 0 8	7 0 8	7 2 6	7 2 9	7 2 9	
Carcass ID Number	1 7 1	1 6 3	1 7 2	1 9 4	1 5 9	1 6 4	1 7 7	1 6 7	1 9 9	1 7 8	1 9 6	1 9 5	1 8 6	1 8 7	1 7 0	1 5 1	1 5 4	1 5 7	1 6 5	1 8 4	1 8 5	1 9 3	1 8 3	1 6 9	1 7 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, transitional epithelium, carcinoma																										1
Renal tubule, adenoma	X																X	X								4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X	X	X						X	X						X	X	X	X	X	X	24

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	8/50 (16%)	5/49 (10%)	8/50 (16%)	3/50 (6%)
Adjusted rate[b]	18.9%	12.1%	18.0%	9.2%
Terminal rate[c]	4/22 (18%)	3/27 (11%)	6/31 (19%)	0/2 (0%)
First incidence (days)	690	673	708	624
Poly-3 test[d]	P=0.235N	P=0.290N	P=0.568N	P=0.199N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	8/50 (16%)	5/49 (10%)	10/50 (20%)	4/50 (8%)
Adjusted rate	18.9%	12.1%	22.5%	12.0%
Terminal rate	4/22 (18%)	3/27 (11%)	8/31 (26%)	0/2 (0%)
First incidence (days)	690	673	708	507
Poly-3 test	P=0.405N	P=0.290N	P=0.439	P=0.310**N**
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	1/50 (2%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	2.4%	4.5%	12.1%
Terminal rate	0/22 (0%)	1/27 (4%)	1/31 (3%)	0/2 (0%)
First incidence (days)	709	729 (T)	687	537
Poly-3 test	P=0.046	P=0.758	P=0.519	P=0.114
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted rate	2.4%	2.4%	11.2%	12.1%
Terminal rate	0/22 (0%)	1/27 (4%)	4/31 (13%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	624
Poly-3 test	P=0.034	P=0.757	P=0.114	P=0.113
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	2/50 (4%)	7/50 (14%)	8/50 (16%)
Adjusted rate	4.7%	4.8%	15.6%	23.3%
Terminal rate	0/22 (0%)	2/27 (7%)	5/31 (16%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	537
Poly-3 test	P=0.004	P=0.688	P=0.093	P=0.017
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	4.8%	4.5%	12.1%
Terminal rate	0/22 (0%)	2/27 (7%)	1/31 (3%)	0/2 (0%)
First incidence (days)	709	729 (T)	687	537
Poly-3 test	P=0.073	P=0.495	P=0.519	P=0.114
Kidney (Renal Tubule): Adenoma or Carcinoma (Step Sections)				
Overall rate	1/50 (2%)	2/50 (4%)	5/50 (10%)	4/50 (8%)
Adjusted rate	2.4%	4.8%	11.2%	12.1%
Terminal rate	0/22 (0%)	2/27 (7%)	4/31 (13%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	624
Poly-3 test	P=0.052	P=0.494	P=0.114	P=0.113
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	2/50 (4%)	3/50 (6%)	7/50 (14%)	8/50 (16%)
Adjusted rate	4.7%	7.2%	15.6%	23.3%
Terminal rate	0/22 (0%)	3/27 (11%)	5/31 (16%)	0/2 (0%)
First incidence (days)	680	729 (T)	590	537
Poly-3 test	P=0.006	P=0.491	P=0.093	P=0.017

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	1/49 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	9.4%	2.4%	0.0%	0.0%
Terminal rate	2/22 (9%)	0/27 (0%)	0/31 (0%)	0/2 (0%)
First incidence (days)	666	704	—[e]	—
Poly-3 test	P=0.017N	P=0.188N	P=0.055N	P=0.105N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	1/49 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate	9.4%	2.4%	2.3%	6.2%
Terminal rate	2/22 (9%)	0/27 (0%)	0/31 (0%)	0/2 (0%)
First incidence (days)	666	704	687	637
Poly-3 test	P=0.332N	P=0.188N	P=0.164N	P=0.467N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	10/50 (20%)	6/50 (12%)	12/50 (24%)	5/50 (10%)
Adjusted rate	23.0%	14.2%	26.2%	14.8%
Terminal rate	1/22 (5%)	3/27 (11%)	6/31 (19%)	0/2 (0%)
First incidence (days)	584	535	499	569
Poly-3 test	P=0.384N	P=0.219N	P=0.456	P=0.272N
Preputial Gland: Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	1/49 (2%)
Adjusted rate	0.0%	7.1%	2.3%	3.2%
Terminal rate	0/22 (0%)	2/27 (7%)	1/31 (3%)	0/2 (0%)
First incidence (days)	—	543	729 (T)	726
Poly-3 test	P=0.461	P=0.118	P=0.510	P=0.442
Preputial Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/49 (2%)
Adjusted rate	2.4%	7.2%	6.6%	3.1%
Terminal rate	1/22 (5%)	2/27 (7%)	1/31 (3%)	0/2 (0%)
First incidence (days)	729 (T)	709	543	569
Poly-3 test	P=0.529	P=0.301	P=0.332	P=0.696
Preputial Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	4/50 (8%)	2/49 (4%)
Adjusted rate	2.4%	14.2%	8.8%	6.3%
Terminal rate	1/22 (5%)	4/27 (15%)	2/31 (7%)	0/2 (0%)
First incidence (days)	729 (T)	543	543	569
Poly-3 test	P=0.440	P=0.055	P=0.201	P=0.405
Skin: Keratoacanthoma				
Overall rate	10/50 (20%)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rate	23.2%	7.1%	6.7%	9.1%
Terminal rate	4/22 (18%)	0/27 (0%)	2/31 (7%)	0/2 (0%)
First incidence (days)	584	590	669	537
Poly-3 test	P=0.047N	P=0.035N	P=0.028N	P=0.093N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	11/50 (22%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate	25.5%	11.8%	6.7%	9.1%
Terminal rate	4/22 (18%)	2/27 (7%)	2/31 (7%)	0/2 (0%)
First incidence (days)	584	590	669	537
Poly-3 test	P=0.021N	P=0.086N	P=0.015N	P=0.061N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Skin: Basal Cell Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	7.2%	2.3%	0.0%
Terminal rate	0/22 (0%)	2/27 (7%)	1/31 (3%)	0/2 (0%)
First incidence (days)	—	609	729 (T)	—[f]
Poly-3 test	P=0.454N	P=0.118	P=0.510	—
Skin: Trichoepithelioma or Basal Cell Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	0.0%	7.2%	4.5%	0.0%
Terminal rate	0/22 (0%)	2/27 (7%)	2/31 (7%)	0/2 (0%)
First incidence (days)	—	609	729 (T)	—
Poly-3 test	P=0.534N	P=0.118	P=0.249	—
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	11/50 (22%)	8/50 (16%)	5/50 (10%)	3/50 (6%)
Adjusted rate	25.5%	18.7%	11.2%	9.1%
Terminal rate	4/22 (18%)	4/27 (15%)	4/31 (13%)	0/2 (0%)
First incidence (days)	584	590	669	537
Poly-3 test	P=0.027N	P=0.307N	P=0.070N	P=0.061N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	5/50 (10%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	11.8%	7.2%	6.8%	6.1%
Terminal rate	3/22 (14%)	0/27 (0%)	2/31 (7%)	0/2 (0%)
First incidence (days)	680	704	687	555
Poly-3 test	P=0.245N	P=0.364N	P=0.330N	P=0.329N
Skin (Subcutaneous Tissue): Fibroma or Fibrous Histiocytoma				
Overall rate	6/50 (12%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	14.2%	7.2%	6.8%	6.1%
Terminal rate	3/22 (14%)	0/27 (0%)	2/31 (7%)	0/2 (0%)
First incidence (days)	680	704	687	555
Poly-3 test	P=0.158N	P=0.248N	P=0.218N	P=0.228N
Testes: Adenoma				
Overall rate	45/50 (90%)	46/50 (92%)	46/50 (92%)	48/50 (96%)
Adjusted rate	93.2%	98.0%	95.5%	98.1%
Terminal rate	22/22 (100%)	27/27 (100%)	31/31 (100%)	2/2 (100%)
First incidence (days)	495	484	486	487
Poly-3 test	P=0.172	P=0.219	P=0.473	P=0.203
Thyroid Gland (C-cell): Adenoma				
Overall rate	10/50 (20%)	6/50 (12%)	9/50 (18%)	4/50 (8%)
Adjusted rate	23.3%	14.4%	20.2%	12.1%
Terminal rate	5/22 (23%)	5/27 (19%)	6/31 (19%)	0/2 (0%)
First incidence (days)	638	715	691	621
Poly-3 test	P=0.197N	P=0.221N	P=0.462N	P=0.171N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	11/50 (22%)	8/50 (16%)	10/50 (20%)	5/50 (10%)
Adjusted rate	25.6%	19.2%	22.4%	15.1%
Terminal rate	6/22 (27%)	7/27 (26%)	7/31 (23%)	0/2 (0%)
First incidence (days)	638	715	691	621
Poly-3 test	P=0.205N	P=0.327N	P=0.459N	P=0.201N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	4.7%	4.8%	6.7%	8.9%
Terminal rate	1/22 (5%)	0/27 (0%)	2/31 (7%)	0/2 (0%)
First incidence (days)	634	709	613	487
Poly-3 test	P=0.272	P=0.688	P=0.524	P=0.398
All Organs: Mononuclear Cell Leukemia				
Overall rate	27/50 (54%)	41/50 (82%)	39/50 (78%)	24/50 (48%)
Adjusted rate	55.8%	82.3%	81.2%	59.3%
Terminal rate	6/22 (27%)	20/27 (74%)	25/31 (81%)	2/2 (100%)
First incidence (days)	425	344	494	487
Poly-3 test	P=0.508	P=0.003	P=0.005	P=0.454
All Organs: Malignant Mesothelioma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	4.7%	7.1%	4.5%	0.0%
Terminal rate	1/22 (5%)	2/27 (7%)	0/31 (0%)	0/2 (0%)
First incidence (days)	549	590	624	—
Poly-3 test	P=0.203N	P=0.493	P=0.677N	P=0.306N
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	47/50 (94%)	49/50 (98%)	50/50 (100%)
Adjusted rate	99.6%	98.8%	99.4%	100.0%
Terminal rate	22/22 (100%)	27/27 (100%)	31/31 (100%)	2/2 (100%)
First incidence (days)	495	484	486	487
Poly-3 test	P=0.655	P=0.932N	P=0.991N	P=1.000
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	42/50 (84%)	40/50 (80%)	26/50 (52%)
Adjusted rate	66.7%	84.3%	82.7%	62.5%
Terminal rate	9/22 (41%)	21/27 (78%)	25/31 (81%)	2/2 (100%)
First incidence (days)	425	344	494	487
Poly-3 test	P=0.275N	P=0.033	P=0.053	P=0.417N
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	22/22 (100%)	27/27 (100%)	31/31 (100%)	2/2 (100%)
First incidence (days)	425	344	486	487
Poly-3 test	—	—	—	—

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

TABLE A4a
Historical Incidence of Renal Tubule Adenoma in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	1/50
Citral	0/100
p,p'-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	0/100
2-Methylimidazole	0/49
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Step sections	
Stoddard solvent IIC	
Single	0/50
Step section	3/50
Total	3/50
Propylene glycol mono-*t*-butyl ether	
Single	1/50
Step section	0/50
Total	1/50
Overall Total	4/100
Overall Historical Incidence: Feed Studies	
Total (%)	1/459 (0.2%)
Mean ± standard deviation	0.3% ± 0.8%
Range	0%-2%
Overall Historical Incidence: All Routes	
Total (%)	5/1,152 (0.4%)
Mean ± standard deviation	0.5% ± 0.9%
Range	0%-2%

[a] Data as of April 19, 2004

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	27/50
Citral	68/100
p,p'-Dichlorodiphenyl sulfone	27/50
trans-Cinnamaldehyde	40/100
2-Methylimidazole	15/50
o-Nitrotoluene	30/60
p-Nitrotoluene	24/50
Overall Historical Incidence: Feed Studies	
Total (%)	231/460 (50.2%)
Mean ± standard deviation	49.1% ± 11.9%
Range	30%-68%
Overall Historical Incidence: All Routes	
Total (%)	514/1,159 (44.4%)
Mean ± standard deviation	43.1% ± 12.8%
Range	22%-68%

[a] Data as of April 19, 2004

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone[a]

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	25	12	16	44
Natural deaths	3	11	3	4
Survivors				
Terminal sacrifice	22	27	31	2
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Erosion			1 (2%)	
Inflammation			1 (2%)	
Parasite metazoan	1 (2%)	1 (2%)	1 (2%)	
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	6 (12%)	6 (12%)	8 (16%)	5 (10%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Erosion	1 (2%)		1 (2%)	1 (2%)
Inflammation				4 (8%)
Mineralization				2 (4%)
Ulcer				1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Basophilic focus	24 (48%)	25 (50%)	32 (64%)	19 (38%)
Clear cell focus	19 (38%)	19 (38%)	18 (36%)	
Congestion	1 (2%)			
Degeneration, cystic	8 (16%)	11 (22%)	20 (40%)	15 (30%)
Eosinophilic focus	5 (10%)	14 (28%)	10 (20%)	9 (18%)
Fatty change, diffuse	22 (44%)	20 (40%)	22 (44%)	15 (30%)
Hematopoietic cell proliferation	4 (8%)	1 (2%)	2 (4%)	4 (8%)
Hepatodiaphragmatic nodule	2 (4%)	6 (12%)	1 (2%)	1 (2%)
Infarct				1 (2%)
Inflammation, chronic active	22 (44%)	21 (42%)	35 (70%)	33 (66%)
Inflammation, granulomatous	1 (2%)			2 (4%)
Mineralization				1 (2%)
Mixed cell focus	9 (18%)	17 (34%)	22 (44%)	4 (8%)
Necrosis	19 (38%)	19 (38%)	9 (18%)	14 (28%)
Bile duct, cyst		1 (2%)		
Bile duct, hyperplasia	49 (98%)	46 (92%)	48 (96%)	50 (100%)
Hepatocyte, multinucleated	1 (2%)		1 (2%)	
Hepatocyte, centrilobular, hypertrophy		17 (34%)	31 (62%)	19 (38%)
Hepatocyte, centrilobular, necrosis				1 (2%)
Vein, inflammation				1 (2%)
Mesentery	(9)	(12)	(8)	(4)
Inflammation	1 (11%)		1 (13%)	1 (25%)
Fat, necrosis	7 (78%)	7 (58%)	7 (88%)	3 (75%)
Oral mucosa	(8)	(8)	(5)	(7)
Gingival, hyperplasia			1 (20%)	
Gingival, inflammation	8 (100%)	6 (75%)	5 (100%)	5 (71%)
Pharyngeal, inflammation				1 (14%)

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Basophilic focus		1 (2%)		
Cyst				3 (6%)
Inflammation	14 (28%)	16 (32%)	6 (12%)	9 (18%)
Metaplasia, hepatocyte				1 (2%)
Acinus, atrophy	20 (40%)	21 (42%)	22 (44%)	10 (20%)
Acinus, hyperplasia	1 (2%)			
Salivary glands	(49)	(50)	(50)	(49)
Atrophy	1 (2%)	1 (2%)	3 (6%)	
Inflammation		2 (4%)		
Stomach, forestomach	(50)	(49)	(49)	(50)
Autolysis		1 (2%)		
Hyperplasia, squamous	7 (14%)	4 (8%)	10 (20%)	17 (34%)
Inflammation	8 (16%)	6 (12%)	8 (16%)	12 (24%)
Mineralization		1 (2%)	1 (2%)	3 (6%)
Ulcer	4 (8%)	1 (2%)	8 (16%)	8 (16%)
Stomach, glandular	(50)	(50)	(49)	(50)
Erosion	5 (10%)	2 (4%)	3 (6%)	3 (6%)
Hyperplasia			1 (2%)	
Inflammation	5 (10%)	5 (10%)	4 (8%)	7 (14%)
Mineralization			5 (10%)	15 (30%)
Ulcer	1 (2%)		1 (2%)	4 (8%)
Tooth	(3)	(5)	(2)	(3)
Inflammation	1 (33%)		1 (50%)	1 (33%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Inflammation			1 (2%)	
Mineralization		1 (2%)	1 (2%)	11 (22%)
Pulmonary artery, pulmonary vein, hypertrophy			1 (2%)	
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	48 (96%)	48 (96%)	47 (94%)	49 (98%)
Mineralization			2 (4%)	6 (12%)
Aorta, tunic, media, mineralization		1 (2%)		
Atrium, thrombosis	3 (6%)	5 (10%)	2 (4%)	1 (2%)
Endocardium, hyperplasia		2 (4%)		
Valve, thrombosis		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Angiectasis	4 (8%)	4 (8%)	2 (4%)	1 (2%)
Atrophy		1 (2%)		
Cytoplasmic alteration	1 (2%)			
Degeneration, cystic	1 (2%)			
Hematopoietic cell proliferation	5 (10%)		2 (4%)	
Hyperplasia	1 (2%)	4 (8%)	11 (22%)	4 (8%)
Hypertrophy	8 (16%)	2 (4%)	3 (6%)	3 (6%)
Necrosis	1 (2%)	4 (8%)		1 (2%)
Vacuolization cytoplasmic	27 (54%)	27 (55%)	31 (62%)	27 (54%)
Adrenal medulla	(50)	(49)	(50)	(50)
Angiectasis		1 (2%)		
Hyperplasia	6 (12%)	8 (16%)	11 (22%)	5 (10%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System (continued)				
Parathyroid gland	(49)	(45)	(48)	(49)
Hyperplasia	2 (4%)	1 (2%)	19 (40%)	32 (65%)
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	4 (8%)	10 (20%)	11 (22%)	3 (6%)
Cyst	6 (12%)	3 (6%)	1 (2%)	5 (10%)
Hyperplasia	16 (32%)	21 (42%)	12 (24%)	13 (26%)
Inflammation		1 (2%)		1 (2%)
Pigmentation, hemosiderin		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell	1 (2%)			
Ultimobranchial cyst			2 (4%)	1 (2%)
C-cell, hyperplasia	17 (34%)	8 (16%)	8 (16%)	5 (10%)
Follicle, cyst		1 (2%)		
Follicle, degeneration	1 (2%)	2 (4%)		
Follicular cell, hyperplasia		1 (2%)		1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)		1 (2%)	2 (4%)
Inflammation	3 (6%)		4 (8%)	1 (2%)
Preputial gland	(50)	(50)	(50)	(49)
Atrophy			1 (2%)	
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Inflammation	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Duct, cyst			1 (2%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)
Atrophy	4 (8%)	7 (14%)	8 (16%)	4 (8%)
Hyperplasia	2 (4%)	3 (6%)	4 (8%)	
Inflammation	18 (36%)	17 (34%)	26 (52%)	26 (52%)
Seminal vesicle	(50)	(50)	(50)	(49)
Atrophy	3 (6%)	7 (14%)	8 (16%)	4 (8%)
Inflammation	1 (2%)		1 (2%)	1 (2%)
Mineralization				4 (8%)
Testes	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		1 (2%)
Necrosis		2 (4%)		
Germinal epithelium, degeneration	6 (12%)	5 (10%)	6 (12%)	7 (14%)
Interstitial cell, hyperplasia	15 (30%)	12 (24%)	14 (28%)	22 (44%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hyperplasia, megakaryocyte		1 (2%)		
Inflammation, granulomatous			1 (2%)	2 (4%)
Myelofibrosis		1 (2%)	2 (4%)	2 (4%)
Necrosis		1 (2%)		
Erythroid cell, hyperplasia	13 (26%)	3 (6%)	10 (20%)	10 (20%)
Myeloid cell, hyperplasia	21 (42%)	27 (55%)	20 (40%)	14 (28%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Hematopoietic System (continued)				
Lymph node	(19)	(20)	(16)	(19)
Deep cervical, ectasia	2 (11%)			1 (5%)
Deep cervical, infiltration cellular, plasma cell	1 (5%)	2 (10%)		2 (11%)
Mediastinal, ectasia	3 (16%)		4 (25%)	3 (16%)
Mediastinal, hemorrhage	1 (5%)		1 (6%)	2 (11%)
Mediastinal, hyperplasia			1 (6%)	2 (11%)
Mediastinal, infiltration cellular, plasma cell		1 (5%)	2 (13%)	3 (16%)
Mediastinal, infiltration cellular, histiocyte	2 (11%)			
Mediastinal, inflammation			1 (6%)	
Pancreatic, ectasia			2 (13%)	2 (11%)
Pancreatic, hemorrhage			1 (6%)	1 (5%)
Pancreatic, infiltration cellular, histiocyte	1 (5%)	1 (5%)	2 (13%)	
Pancreatic, inflammation			3 (19%)	1 (5%)
Renal, ectasia				1 (5%)
Renal, infiltration cellular, histiocyte				1 (5%)
Lymph node, mandibular	(5)	(1)	(2)	
Ectasia	1 (20%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			6 (12%)
Ectasia	4 (8%)	2 (4%)	5 (10%)	4 (8%)
Infiltration cellular, histiocyte	47 (94%)	41 (82%)	48 (96%)	46 (92%)
Inflammation	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Accessory spleen		1 (2%)		
Autolysis		1 (2%)		
Fibrosis	1 (2%)		3 (6%)	1 (2%)
Hematopoietic cell proliferation	45 (90%)	42 (84%)	45 (90%)	41 (82%)
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, lymphoid	6 (12%)	2 (4%)	9 (18%)	4 (8%)
Inflammation, granulomatous	1 (2%)	3 (6%)	7 (14%)	1 (2%)
Necrosis	1 (2%)	2 (4%)		1 (2%)
Pigmentation, hemosiderin	39 (78%)	43 (86%)	44 (88%)	43 (86%)
Lymphoid follicle, atrophy	1 (2%)		1 (2%)	2 (4%)
Thymus	(48)	(48)	(48)	(48)
Atrophy	44 (92%)	42 (88%)	47 (98%)	46 (96%)
Ectopic parathyroid gland		1 (2%)		4 (8%)
Integumentary System				
Mammary gland	(50)	(48)	(50)	(50)
Fibrosis	1 (2%)			
Galactocele	2 (4%)		1 (2%)	
Inflammation	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Inflammation	2 (4%)			
Subcutaneous tissue, inflammation		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)	4 (8%)
Osteosclerosis			1 (2%)	
Skeletal muscle	(2)	(2)	(1)	
Degeneration	1 (50%)	1 (50%)	1 (100%)	
Inflammation	1 (50%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	5 (10%)	5 (10%)	2 (4%)	5 (10%)
Necrosis	2 (4%)	4 (8%)		
Peripheral nerve	(1)			
Infiltration cellular, mononuclear cell	1 (100%)			
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Inflammation, acute	2 (4%)	2 (4%)	5 (10%)	7 (14%)
Inflammation, granulomatous	2 (4%)	4 (8%)	5 (10%)	2 (4%)
Metaplasia, squamous				1 (2%)
Mineralization			2 (4%)	10 (20%)
Necrosis	1 (2%)			
Thrombosis		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	16 (32%)	5 (10%)	13 (26%)	7 (14%)
Alveolus, infiltration cellular, histiocyte	46 (92%)	47 (96%)	49 (98%)	50 (100%)
Bronchiole, hyperplasia	1 (2%)	3 (6%)		
Interstitium, fibrosis		2 (4%)		
Nose	(50)	(50)	(50)	(50)
Inflammation	7 (14%)	7 (14%)	8 (16%)	9 (18%)
Thrombosis	1 (2%)	2 (4%)	1 (2%)	
Olfactory epithelium, degeneration	1 (2%)			
Olfactory epithelium, metaplasia	1 (2%)		1 (2%)	
Respiratory epithelium, hyperplasia	1 (2%)		1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Inflammation	2 (4%)	1 (2%)	8 (16%)	3 (6%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Anterior chamber, inflammation				1 (2%)
Ciliary body, inflammation			1 (2%)	
Cornea, inflammation				1 (2%)
Iris, fibrosis	1 (2%)		1 (2%)	
Iris, inflammation	1 (2%)			1 (2%)
Lens, cataract	2 (4%)		1 (2%)	
Lens, mineralization	1 (2%)			
Retina, atrophy	1 (2%)			
Retina, degeneration	5 (10%)	2 (4%)	5 (10%)	
Harderian gland	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, lymphoid	9 (18%)	4 (8%)	9 (18%)	3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet	4 (8%)	1 (2%)	4 (8%)	2 (4%)
Hyperplasia, oncocytic			1 (2%)	
Infarct	1 (2%)	3 (6%)		
Nephropathy	50 (100%)	45 (90%)	50 (100%)	50 (100%)
Artery, inflammation				1 (2%)
Cortex, mineralization		1 (2%)	4 (8%)	14 (28%)
Medulla, mineralization	47 (94%)	49 (98%)	47 (94%)	49 (98%)
Papilla, transitional epithelium, hyperplasia				1 (2%)
Pelvis, inflammation			1 (2%)	1 (2%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)	11 (22%)	29 (58%)	34 (68%)
Renal tubule, cyst			1 (2%)	9 (18%)
Renal tubule, hyperplasia	1 (2%)	5 (10%)	20 (40%)	23 (46%)
Renal tubule, hyperplasia, oncocytic			1 (2%)	
Renal tubule, pigmentation	1 (2%)	1 (2%)	2 (4%)	
Urinary bladder	(50)	(50)	(50)	(50)
Calculus gross observation		1 (2%)	1 (2%)	
Inflammation	3 (6%)		2 (4%)	2 (4%)
Muscularis, degeneration	1 (2%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF BENZOPHENONE

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	16	10	9	13
Natural deaths	2	2	4	3
Survivors				
Terminal sacrifice	32	38	37	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Schwannoma malignant			1 (2%)	
Intestine small, ileum	(50)	(50)	(50)	(50)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)		
Hepatocellular adenoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	2 (4%)
Mesentery	(12)	(18)	(10)	(6)
Histiocytic sarcoma				1 (17%)
Oral mucosa	(4)	(8)	(4)	(4)
Gingival, squamous cell carcinoma		1 (13%)		
Pancreas	(50)	(50)	(50)	(50)
Salivary glands	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Schwannoma malignant				1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Tooth			(3)	(3)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Endocardium, schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma benign		2 (4%)	2 (4%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			2 (4%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System (continued)				
Parathyroid gland	(47)	(48)	(44)	(48)
Adenoma			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	17 (34%)	17 (34%)	11 (22%)	13 (26%)
Thyroid gland	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Bilateral, C-cell, carcinoma			1 (2%)	
C-cell, adenoma	4 (8%)	6 (12%)	3 (6%)	6 (12%)
C-cell, carcinoma		1 (2%)		1 (2%)
Follicular cell, adenoma				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)		5 (10%)	6 (12%)
Carcinoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Histiocytic sarcoma			1 (2%)	
Squamous cell papilloma	1 (2%)			
Bilateral, adenoma	1 (2%)	1 (2%)		
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor benign				1 (2%)
Histiocytic sarcoma			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Polyp stromal	6 (12%)	9 (18%)	10 (20%)	10 (20%)
Cervix, histiocytic sarcoma				1 (2%)
Cervix, schwannoma malignant				1 (2%)
Vagina		(1)	(1)	
Schwannoma malignant		1 (100%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lymph node	(8)	(8)	(11)	(12)
Deep cervical, carcinoma, metastatic, thyroid gland			1 (9%)	
Lymph node, mandibular		(1)	(1)	(1)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Spleen	(49)	(50)	(50)	(50)
Thymus	(50)	(49)	(46)	(50)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Thymoma malignant		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	2 (4%)	3 (6%)	
Carcinoma		1 (2%)	1 (2%)	
Fibroadenoma	21 (42%)	20 (40%)	12 (24%)	7 (14%)
Fibroadenoma, multiple	6 (12%)	4 (8%)	3 (6%)	
Histiocytic sarcoma			1 (2%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Keratoacanthoma	3 (6%)		2 (4%)	
Lipoma		1 (2%)		
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, fibroma	3 (6%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Musculoskeletal System				
Skeletal muscle	(1)	(1)	(3)	(1)
Histiocytic sarcoma			1 (33%)	1 (100%)
Rhabdomyosarcoma			1 (33%)	
Sarcoma			1 (33%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)		1 (2%)	
Carcinoma, metastatic, thyroid gland			1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)	2 (4%)
Nose	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Histiocytic sarcoma				1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Iris, melanoma benign	1 (2%)			
Zymbal's gland			(1)	(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Renal tubule, adenoma, multiple			2 (4%)	1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	2 (4%)
Leukemia mononuclear	19 (38%)	25 (50%)	30 (60%)	29 (58%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	46	45	44
Total primary neoplasms	93	95	97	85
Total animals with benign neoplasms	42	40	37	33
Total benign neoplasms	71	62	59	48
Total animals with malignant neoplasms	20	29	32	32
Total malignant neoplasms	22	33	38	37
Total animals with metastatic neoplasms			1	1
Total metastatic neoplasms			4	1

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	2 8 8	3 5 8	4 3 0	5 2 8	5 4 3	6 1 3	6 2 4	6 3 4	6 3 7	6 7 3	6 9 7	7 0 8	7 0 8	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	2 4 4	2 4 5	2 4 9	2 1 3	2 4 3	2 0 6	2 1 0	2 1 1	2 1 8	2 2 3	2 3 7	2 1 9	2 2 4	2 2 9	2 3 0	2 3 4	2 4 7	2 2 0	2 0 4	2 0 5	2 0 9	2 2 1	2 2 2	2 4 1	2 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery										+		+		+	+		+		+						
Oral mucosa		+		+											+									+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma malignant																		X							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X						X					X		X	X	X			X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma														X											X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X									X					
Carcinoma														X											
Squamous cell papilloma																							X		
Bilateral, adenoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																			X						

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 0 2	2 0 3	2 0 7	2 0 8	2 1 2	2 1 5	2 1 7	2 2 5	2 3 1	2 3 2	2 3 5	2 3 6	2 3 8	2 3 9	2 4 0	2 1 4	2 1 6	2 2 6	2 2 7	2 2 8	2 3 3	2 4 2	2 4 6	2 4 8	2 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+						+	+		+								+	+				12
Oral mucosa																										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X				X				X	X	X							X				X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X											X							4
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Carcinoma																										1
Squamous cell papilloma																										1
Bilateral, adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X			X					X								X	X	6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	2 8 8	3 5 8	4 3 0	5 2 8	5 4 3	6 1 3	6 2 4	6 3 4	6 3 7	6 7 3	6 9 7	7 0 8	7 0 8	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	2 4 4	2 4 5	2 4 9	2 1 3	2 4 3	2 0 6	2 1 0	2 1 1	2 1 8	2 2 3	2 3 7	2 1 9	2 2 4	2 2 9	2 3 0	2 3 4	2 4 7	2 2 0	2 0 4	2 0 5	2 0 9	2 2 1	2 2 2	2 4 1	2 0 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+			+	+	+	+			+	+								
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																								
Fibroadenoma				X				X	X	X			X						X	X		X		X	
Fibroadenoma, multiple						X						X						X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma								X							X										
Subcutaneous tissue, fibroma															X					X					
Subcutaneous tissue, fibrosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iris, melanoma benign					X																				
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X	X	X	X		X				X	X		X	X		X	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 0 2	2 0 3	2 0 7	2 0 8	2 1 2	2 1 5	2 1 7	2 2 5	2 3 1	2 3 2	2 3 5	2 3 6	2 3 8	2 3 9	2 4 0	2 1 4	2 1 6	2 2 6	2 2 7	2 2 8	2 3 3	2 4 2	2 4 6	2 4 8	2 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										8
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								2
Fibroadenoma		X	X	X	X		X	X		X			X		X						X			X	X	21
Fibroadenoma, multiple						X										X				X						6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																				X						3
Subcutaneous tissue, fibroma																					X					3
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X			X									X				X			4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iris, melanoma benign																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X	X		X	X						X	X		X	X						19

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	6 0 9	6 1 3	6 1 3	6 3 3	6 5 3	6 9 0	6 9 3	6 9 7	6 9 7	7 1 0	7 2 5	7 2 5	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 8 8	2 6 4	2 9 7	2 5 6	2 6 2	2 9 5	2 7 1	2 7 2	2 7 9	2 8 7	2 5 9	2 9 6	2 5 8	2 8 5	2 9 3	3 0 0	2 5 1	2 6 1	2 6 5	2 6 7	2 6 8	2 6 9	2 7 0	2 7 3	2 7 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery						+	+	+	+	+			+	+	+			+	+						+
Oral mucosa	+					+								+					+						
Gingival, squamous cell carcinoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	X	X			X		X			X			X		X			X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X				X		X								
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal				X		X							X			X						X		X	
Vagina	+																								
Schwannoma malignant	X																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	27 8	28 2	28 6	29 1	29 2	29 4	29 9	25 2	25 3	25 4	25 5	25 7	26 0	26 3	26 6	27 4	27 6	27 7	28 0	28 1	28 3	28 4	28 9	29 0	29 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																X										1
Mesentery	+	+	+						+	+			+									+				18
Oral mucosa		+	+	+								+														8
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma										X		X			X		X					X		X	X	17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X												X			X		6
C-cell, carcinoma											X															1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																				X	X					2
Bilateral, adenoma																									X	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal							X					X						X								9
Vagina																										1
Schwannoma malignant																										1

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	1	1	3	5	9	9	9	9	1	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3
	9	3	3	3	3	0	3	7	7	0	5	5	9	9	9	9	0	0	0	0	0	0	0	0	0
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2
Carcass ID Number	8	6	9	5	6	9	7	7	7	8	5	9	5	8	9	0	5	6	6	6	6	6	7	7	7
	8	4	7	6	2	5	1	2	9	7	9	6	8	5	3	0	1	1	5	7	8	9	0	3	5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+	+				+	+							+				+			+
Lymph node, mandibular	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Carcinoma													X												
Fibroadenoma								X	X	X		X	X			X		X		X	X	X	X		
Fibroadenoma, multiple							X				X						X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear							+																		
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X			X		X			X			X	X			X	X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 7 8	2 8 2	2 8 6	2 9 1	2 9 2	2 9 4	2 9 9	2 5 2	2 5 3	2 5 4	2 5 5	2 5 7	2 6 0	2 6 3	2 6 6	2 7 4	2 7 6	2 7 7	2 8 0	2 8 1	2 8 3	2 8 4	2 8 9	2 9 0	2 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										8
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma malignant	X																									1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														2
Carcinoma																										1
Fibroadenoma	X			X	X							X		X		X			X	X					X	20
Fibroadenoma, multiple							X																			4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X		X	X		X	X						X			X		X	X	X	X	X	25

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 5	3 1 6	3 1 7	3 2 4	3 2 8	3 3 3	3 3 6	3 3 7	3 4 2	3 4 3	3 4 4	3 4 7	3 0 3	3 0 9	3 1 2	3 1 9	3 2 0	3 2 2	3 2 5	3 2 6	3 3 4	3 3 9	3 4 1	3 4 6	3 4 8	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									1
Histiocytic sarcoma																									1
Mesentery				+							+					+		+		+	+		+		10
Oral mucosa																									4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Tooth										+											+				3
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign												X													2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									2
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	44
Adenoma																									1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X						X				X		X									11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																									1
Bilateral, C-cell, carcinoma												X													1
C-cell, adenoma							X									X						X			3
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	5 2 8	6 0 9	6 3 3	6 4 4	6 6 2	6 7 9	6 9 0	6 9 9	7 0 1	7 0 4	7 0 9	7 0 9	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 0 1	3 3 2	3 2 9	3 1 0	3 0 5	3 3 0	3 4 5	3 1 8	3 4 9	3 3 8	3 0 7	3 3 5	3 4 0	3 1 1	3 1 3	3 2 1	3 2 3	3 2 7	3 3 1	3 5 0	3 0 2	3 0 4	3 0 6	3 0 8	3 1 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma												X													
Histiocytic sarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X							X											X	X			
Vagina																			+						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Lymph node		+	+	+	+					+	+		+						+			+			
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Histiocytic sarcoma	X																								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X					X														
Carcinoma											X														
Fibroadenoma		X									X			X				X	X	X	X				
Fibroadenoma, multiple					X																				
Histiocytic sarcoma	X																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Keratoacanthoma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+								+					+											
Histiocytic sarcoma	X																								
Rhabdomyosarcoma														X											
Sarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 5	3 1 6	3 1 7	3 2 4	3 2 8	3 3 3	3 3 6	3 3 7	3 4 2	3 4 3	3 4 4	3 4 7	3 0 3	3 0 9	3 1 2	3 1 9	3 2 0	3 2 2	3 2 5	3 2 6	3 3 4	3 3 9	3 4 1	3 4 6	3 4 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X				X									X				X						5
Carcinoma																				X						2
Histiocytic sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal		X							X	X		X			X					X						10
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node				+								+														11
Deep cervical, carcinoma, metastatic, thyroid gland												X														1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	46
Carcinoma, metastatic, thyroid gland												X														1
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									3
Carcinoma																										1
Fibroadenoma				X		X				X													X		X	12
Fibroadenoma, multiple	X																	X								3
Histiocytic sarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Keratoacanthoma								X																		2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Histiocytic sarcoma																										1
Rhabdomyosarcoma																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	5 2 8	6 0 9	6 3 3	6 4 4	6 6 2	6 7 9	6 9 0	6 9 9	7 0 1	7 0 4	7 0 9	7 0 9	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	3 0 1	3 3 2	3 2 9	3 1 0	3 0 5	3 3 0	3 4 5	3 1 8	3 4 9	3 3 8	3 0 7	3 3 5	3 4 0	3 1 1	3 1 3	3 2 1	3 2 3	3 2 7	3 3 1	3 5 0	3 0 2	3 0 4	3 0 6	3 0 8	3 1 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland																									
Histiocytic sarcoma	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Special Senses System																									
Ear											+			+											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland			+																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma, multiple									X			X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Leukemia mononuclear		X	X	X	X			X	X		X	X	X	X		X		X	X		X				X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 1 5	3 1 6	3 1 7	3 2 4	3 2 8	3 3 3	3 3 6	3 3 7	3 4 2	3 4 3	3 4 4	3 4 7	3 0 3	3 0 9	3 1 2	3 1 9	3 2 0	3 2 2	3 2 5	3 2 6	3 3 4	3 3 9	3 4 1	3 4 6	3 4 8	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									1
Carcinoma, metastatic, thyroid gland												X														1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland												X														1
Special Senses System																										
Ear																					+					3
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma, multiple																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear		X	X	X			X		X	X		X			X		X	X			X	X	X	X		X	30

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	480	528	581	624	638	653	655	679	709	708	716	768	701	709	711	725	729	729	729	729	729	729	729	729	729
Carcass ID Number	385	369	374	388	351	396	381	382	400	372	361	667	622	725	776	793	553	589	644	673	703	899	911	999	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X		X																						
Mesentery			+																						
Histiocytic sarcoma			X																						
Oral mucosa				+								+			+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+								+													
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X						X	X					X	X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma	X														X	X							X		
C-cell, carcinoma																									
Follicular cell, adenoma																						X			
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 5 5 6	3 6 3	3 6 6	3 7 7	3 8 3	3 8 4	3 8 6	3 8 7	3 9 0	3 5 2	3 5 4	3 5 5	3 5 7	3 6 0	3 6 5	3 6 8	3 7 0	3 7 1	3 7 8	3 7 9	3 9 2	3 9 4	3 9 5	3 9 7	3 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Mesentery							+				+	+				+	+									6
Histiocytic sarcoma																										1
Oral mucosa	+																									4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant	X																									1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth								+																		3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X						X					X				X	X						X	13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X												X												6
C-cell, carcinoma									X																	1
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	480	528	581	624	638	653	655	679	709	708	686	687	701	709	711	725	729	729	729	729	729	729	729	729
Carcass ID Number	385	369	374	388	351	396	381	382	400	372	361	367	362	375	376	393	353	558	589	643	733	780	891	999
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X		X								X										
Carcinoma																								X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																							X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X					X							X			X		X	
Cervix, histiocytic sarcoma	X																							
Cervix, schwannoma malignant		X																						
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+		+	+	+		+		+		+	+	+								
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma											X	X	X	X										X
Histiocytic sarcoma			X																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																					
Histiocytic sarcoma			X																					
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																								
Histiocytic sarcoma	X		X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																							
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																								
Carcinoma																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 5 5 6	3 6 3	3 6 6	3 7 7	3 8 3	3 8 4	3 8 6	3 8 7	3 9 0	3 5 2	3 5 4	3 5 5	3 5 7	3 6 0	3 6 5	3 6 8	3 7 0	3 7 1	3 7 8	3 7 9	3 9 2	3 9 4	3 9 5	3 9 7	3 9 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X			X														X					6
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal										X							X	X			X				X	10
Cervix, histiocytic sarcoma																										1
Cervix, schwannoma malignant																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+										+							+						12
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma								X			X															7
Histiocytic sarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma					X																					1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Histiocytic sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland									X																	1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland										+																1
Carcinoma										X																1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	480	528	581	624	638	653	655	679	679	681	686	687	701	709	711	725	729	729	729	729	729	729	729	729
Carcass ID Number	385	369	374	388	351	396	381	382	400	402	361	367	362	375	376	393	353	358	359	364	373	389	391	399
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																					
Renal tubule, adenoma, multiple									X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																					
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X		X																					
Leukemia mononuclear	X	X		X	X	X		X		X		X			X			X	X		X	X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	35 6	36 3	36 6	37 7	38 3	38 4	38 6	38 7	39 0	35 2	35 4	35 5	35 7	36 0	36 5	36 8	37 0	37 1	37 8	37 9	39 2	39 4	39 5	39 7	39 8	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma, multiple																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Leukemia mononuclear		X	X		X			X	X	X	X		X			X	X			X	X	X			X	29

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Clitoral Gland: Adenoma				
Overall rate[a]	3/50 (6%)	1/50 (2%)	5/50 (10%)	6/50 (12%)
Adjusted rate[b]	6.8%	2.1%	10.6%	12.9%
Terminal rate[c]	2/32 (6%)	1/38 (3%)	5/37 (14%)	3/34 (9%)
First incidence (days)	697	729 (T)	729 (T)	624
Poly-3 test[d]	P=0.083	P=0.280N	P=0.393	P=0.267
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	6/50 (12%)	7/50 (14%)
Adjusted rate	9.0%	6.3%	12.7%	15.1%
Terminal rate	2/32 (6%)	3/38 (8%)	5/37 (14%)	4/34 (12%)
First incidence (days)	697	729 (T)	709	624
Poly-3 test	P=0.142	P=0.462N	P=0.412	P=0.290
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	0.0%	4.2%	2.2%
Terminal rate	1/32 (3%)	0/38 (0%)	0/37 (0%)	0/34 (0%)
First incidence (days)	708	—[e]	701	679
Poly-3 test	P=0.343N	P=0.106N	P=0.468N	P=0.292N
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	0.0%	4.2%	2.2%
Terminal rate	1/32 (3%)	0/38 (0%)	0/37 (0%)	0/34 (0%)
First incidence (days)	708	—	701	679
Poly-3 test	P=0.343N	P=0.106N	P=0.468N	P=0.292N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.1%	0.0%	2.1%	0.0%
Terminal rate	4/32 (13%)	0/38 (0%)	1/37 (3%)	0/34 (0%)
First incidence (days)	729 (T)	—	729 (T)	—
Poly-3 test	P=0.040N	P=0.051N	P=0.159N	P=0.056N
Mammary Gland: Fibroadenoma				
Overall rate	27/50 (54%)	24/50 (48%)	15/50 (30%)	7/50 (14%)
Adjusted rate	58.4%	50.0%	31.3%	15.1%
Terminal rate	19/32 (59%)	18/38 (47%)	12/37 (32%)	3/34 (9%)
First incidence (days)	528	693	609	686
Poly-3 test	P<0.001N	P=0.269N	P=0.006N	P<0.001N
Mammary Gland: Adenoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.4%	4.2%	6.3%	0.0%
Terminal rate	1/32 (3%)	1/38 (3%)	1/37 (3%)	0/34 (0%)
First incidence (days)	288	633	679	—
Poly-3 test	P=0.199N	P=0.672N	P=0.524	P=0.234N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	28/50 (56%)	25/50 (50%)	17/50 (34%)	7/50 (14%)
Adjusted rate	59.4%	51.7%	35.3%	15.1%
Terminal rate	19/32 (59%)	18/38 (47%)	13/37 (35%)	3/34 (9%)
First incidence (days)	288	633	609	686
Poly-3 test	P<0.001N	P=0.291N	P=0.013N	P<0.001N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	4.4%	6.3%	6.3%	0.0%
Terminal rate	1/32 (3%)	2/38 (5%)	1/37 (3%)	0/34 (0%)
First incidence (days)	288	633	679	—
Poly-3 test	P=0.162N	P=0.527	P=0.524	P=0.234N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	28/50 (56%)	25/50 (50%)	17/50 (34%)	7/50 (14%)
Adjusted rate	59.4%	51.7%	35.3%	15.1%
Terminal rate	19/32 (59%)	18/38 (47%)	13/37 (35%)	3/34 (9%)
First incidence (days)	288	633	609	686
Poly-3 test	P<0.001N	P=0.291N	P=0.013N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	17/50 (34%)	17/50 (34%)	11/50 (22%)	13/50 (26%)
Adjusted rate	37.2%	34.8%	23.0%	28.1%
Terminal rate	12/32 (38%)	11/38 (29%)	8/37 (22%)	10/34 (29%)
First incidence (days)	430	613	644	659
Poly-3 test	P=0.157N	P=0.488N	P=0.100N	P=0.239N
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.7%	0.0%	4.2%	0.0%
Terminal rate	1/32 (3%)	0/38 (0%)	1/37 (3%)	0/34 (0%)
First incidence (days)	634	—	701	—
Poly-3 test	P=0.128N	P=0.107N	P=0.472N	P=0.114N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.7%	0.0%	4.2%	2.2%
Terminal rate	1/32 (3%)	0/38 (0%)	1/37 (3%)	1/34 (3%)
First incidence (days)	634	—	701	729 (T)
Poly-3 test	P=0.344N	P=0.107N	P=0.472N	P=0.295N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.8%	0.0%	0.0%	0.0%
Terminal rate	2/32 (6%)	0/38 (0%)	0/37 (0%)	0/34 (0%)
First incidence (days)	724	—	—	—
Poly-3 test	P=0.048N	P=0.106N	P=0.107N	P=0.112N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	4/50 (8%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	9.1%	0.0%	0.0%	0.0%
Terminal rate	2/32 (6%)	0/38 (0%)	0/37 (0%)	0/34 (0%)
First incidence (days)	724	—	—	—
Poly-3 test	P=0.020N	P=0.052N	P=0.052N	P=0.056N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/50 (8%)	6/50 (12%)	3/50 (6%)	6/50 (12%)
Adjusted rate	9.1%	12.6%	6.4%	12.9%
Terminal rate	3/32 (9%)	5/38 (13%)	3/37 (8%)	3/34 (9%)
First incidence (days)	724	725	729 (T)	480
Poly-3 test	P=0.415	P=0.417	P=0.463N	P=0.403

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	7/50 (14%)	4/50 (8%)	7/50 (14%)
Adjusted rate	9.1%	14.7%	8.5%	15.0%
Terminal rate	3/32 (9%)	6/38 (16%)	4/37 (11%)	4/34 (12%)
First incidence (days)	724	725	729 (T)	480
Poly-3 test	P=0.325	P=0.305	P=0.606N	P=0.292
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	9/50 (18%)	10/50 (20%)	10/50 (20%)
Adjusted rate	13.6%	18.8%	21.0%	21.6%
Terminal rate	6/32 (19%)	7/38 (18%)	8/37 (22%)	8/34 (24%)
First incidence (days)	729 (T)	633	633	653
Poly-3 test	P=0.218	P=0.350	P=0.257	P=0.234
All Organs: Mononuclear Cell Leukemia				
Overall rate	19/50 (38%)	25/50 (50%)	30/50 (60%)	29/50 (58%)
Adjusted rate	42.3%	51.5%	61.3%	59.6%
Terminal rate	13/32 (41%)	19/38 (50%)	21/37 (57%)	20/34 (59%)
First incidence (days)	637	613	609	480
Poly-3 test	P=0.058	P=0.247	P=0.048	P=0.068
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	40/50 (80%)	37/50 (74%)	33/50 (66%)
Adjusted rate	86.2%	81.3%	75.4%	68.5%
Terminal rate	27/32 (84%)	30/38 (79%)	28/37 (76%)	22/34 (65%)
First incidence (days)	288	613	609	480
Poly-3 test	P=0.016N	P=0.351N	P=0.130N	P=0.028N
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	29/50 (58%)	32/50 (64%)	32/50 (64%)
Adjusted rate	44.5%	59.2%	64.4%	65.1%
Terminal rate	13/32 (41%)	22/38 (58%)	21/37 (57%)	22/34 (65%)
First incidence (days)	637	609	528	480
Poly-3 test	P=0.041	P=0.109	P=0.039	P=0.033
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	46/50 (92%)	45/50 (90%)	44/50 (88%)
Adjusted rate	94.4%	92.0%	90.0%	88.0%
Terminal rate	30/32 (94%)	34/38 (90%)	32/37 (87%)	28/34 (82%)
First incidence (days)	288	609	528	480
Poly-3 test	P=0.167N	P=0.473N	P=0.330N	P=0.221N

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

TABLE B4a
Historical Incidence of Renal Tubule Adenoma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	0/50
Citral	1/100
p,p′-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	0/100
2-Methylimidazole	0/50
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Overall Historical Incidence: Feed Studies	
Total (%)	1/460 (0.2%)
Mean ± standard deviation	0.1% ± 0.4%
Range	0%-1%
Overall Historical Incidence: All Routes	
Total (%)	1/1,205 (0.1%)
Mean ± standard deviation	0.1% ± 0.2%
Range	0%-1%

[a] Data as of April 19, 2004

TABLE B4b
Historical Incidence of Mononuclear Cell Leukemia and Histiocytic Sarcoma in Untreated Female F344/N Rats[a]

Study	Incidence in Controls	
	Mononuclear Cell Leukemia	Histiocytic Sarcoma
Historical Incidence in Feed Controls Given NTP-2000 Diet		
Benzophenone	19/50	0/50
Citral	24/100	0/100
p,p′-Dichlorodiphenyl sulfone	8/50	0/50
trans-Cinnamaldehyde	21/100	0/100
2-Methylimidazole	6/50	0/50
o-Nitrotoluene	21/60	0/60
p-Nitrotoluene	13/50	0/50
Overall Historical Incidence: Feed Studies		
Total	112/460 (24.4%)	0/460
Mean ± standard deviation	24.6% ± 9.5%	
Range	12%-38%	
Overall Historical Incidence: All Routes		
Total (%)	330/1,209 (27.3%)	1/1,209 (0.1%)
Mean ± standard deviation	28.0% ± 11.2%	0.1% ± 0.4%
Range	12%-52%	0%-2%

[a] Data as of April 19, 2004

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	16	10	9	13
Natural deaths	2	2	4	3
Survivors				
Terminal sacrifice	32	38	37	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		
Periesophageal tissue, necrosis, fatty		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(50)
Inflammation	1 (2%)			
Metaplasia, mucous	1 (2%)			
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	8 (16%)	8 (16%)	14 (28%)	6 (12%)
Ulcer		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		
Mineralization			1 (2%)	
Intestine small, duodenum	(50)	(50)	(50)	(50)
Hyperplasia				1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Inflammation		1 (2%)	2 (4%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	5 (10%)	1 (2%)
Basophilic focus	48 (96%)	48 (96%)	41 (82%)	43 (86%)
Clear cell focus	15 (30%)	13 (26%)	10 (20%)	10 (20%)
Degeneration, cystic	1 (2%)		3 (6%)	4 (8%)
Eosinophilic focus		6 (12%)	6 (12%)	9 (18%)
Fatty change, diffuse	11 (22%)	8 (16%)	9 (18%)	20 (40%)
Fibrosis				1 (2%)
Hematopoietic cell proliferation	1 (2%)	6 (12%)	4 (8%)	2 (4%)
Hepatodiaphragmatic nodule	5 (10%)	6 (12%)	6 (12%)	6 (12%)
Inflammation, chronic active	46 (92%)	38 (76%)	29 (58%)	30 (60%)
Mixed cell focus	10 (20%)	11 (22%)	5 (10%)	5 (10%)
Necrosis	12 (24%)	6 (12%)	11 (22%)	12 (24%)
Bile duct, cyst				1 (2%)
Bile duct, hyperplasia	10 (20%)	35 (70%)	39 (78%)	40 (80%)
Hepatocyte, centrilobular, hypertrophy		27 (54%)	30 (60%)	33 (66%)
Oval cell, hyperplasia				3 (6%)
Mesentery	(12)	(18)	(10)	(6)
Fat, necrosis	11 (92%)	18 (100%)	10 (100%)	4 (67%)
Oral mucosa	(4)	(8)	(4)	(4)
Hyperplasia, squamous				1 (25%)
Gingival, inflammation	4 (100%)	7 (88%)	4 (100%)	4 (100%)

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Basophilic focus			1 (2%)	1 (2%)
Inflammation	12 (24%)	3 (6%)	2 (4%)	6 (12%)
Acinus, atrophy	17 (34%)	10 (20%)	11 (22%)	12 (24%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	2 (4%)		1 (2%)	1 (2%)
Basophilic focus	1 (2%)		1 (2%)	
Inflammation			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, squamous	2 (4%)	2 (4%)	2 (4%)	4 (8%)
Inflammation	4 (8%)	2 (4%)	2 (4%)	3 (6%)
Ulcer		1 (2%)	1 (2%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion		1 (2%)	1 (2%)	1 (2%)
Inflammation			2 (4%)	3 (6%)
Mineralization		2 (4%)	2 (4%)	
Ulcer	1 (2%)			1 (2%)
Epithelium, atrophy			1 (2%)	
Tooth			(3)	(3)
Inflammation			3 (100%)	2 (67%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	46 (92%)	46 (92%)	48 (96%)	46 (92%)
Atrium, thrombosis		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Angiectasis	42 (84%)	36 (72%)	18 (36%)	24 (48%)
Atrophy	1 (2%)			1 (2%)
Degeneration, cystic	3 (6%)	2 (4%)	2 (4%)	
Hematopoietic cell proliferation	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia	6 (12%)	10 (20%)	6 (12%)	6 (12%)
Hypertrophy	7 (14%)	5 (10%)	5 (10%)	8 (16%)
Karyomegaly	1 (2%)			
Necrosis	5 (10%)	7 (14%)	5 (10%)	2 (4%)
Vacuolization cytoplasmic	14 (28%)	16 (32%)	15 (30%)	20 (40%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)	2 (4%)	
Necrosis	2 (4%)			
Vacuolization cytoplasmic	1 (2%)			
Parathyroid gland	(47)	(48)	(44)	(48)
Hyperplasia		1 (2%)		1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Angiectasis	30 (60%)	30 (60%)	23 (46%)	23 (46%)
Cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Hyperplasia	23 (46%)	24 (48%)	20 (40%)	18 (36%)
Inflammation	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	34 (68%)	11 (22%)	13 (26%)	8 (16%)
Follicle, cyst	1 (2%)		1 (2%)	1 (2%)
Follicle, hyperplasia		2 (4%)		
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	
Cyst	3 (6%)	2 (4%)	1 (2%)	
Hyperplasia	6 (12%)	1 (2%)	2 (4%)	
Hyperplasia, squamous				1 (2%)
Inflammation	2 (4%)	2 (4%)	2 (4%)	
Metaplasia, squamous	1 (2%)			
Ovary	(50)	(50)	(50)	(50)
Cyst	6 (12%)	13 (26%)	10 (20%)	9 (18%)
Interstitial cell, hyperplasia		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Angiectasis, focal				1 (2%)
Inflammation				1 (2%)
Cervix, hypertrophy				1 (2%)
Endometrium, hyperplasia, cystic	12 (24%)	20 (40%)	20 (40%)	20 (40%)
Endometrium, hyperplasia, adenomatous	1 (2%)	1 (2%)		1 (2%)
Serosa, inflammation, granulomatous		2 (4%)		
Vagina		(1)	(1)	
Inflammation			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Myelofibrosis	2 (4%)		2 (4%)	6 (12%)
Necrosis			1 (2%)	1 (2%)
Erythroid cell, hyperplasia	8 (16%)	6 (12%)	7 (14%)	2 (4%)
Myeloid cell, hyperplasia	11 (22%)	13 (26%)	20 (40%)	13 (26%)
Lymph node	(8)	(8)	(11)	(12)
Axillary, right, ectasia			1 (9%)	
Axillary, right, infiltration cellular, plasma cell			1 (9%)	
Deep cervical, ectasia	1 (13%)			
Deep cervical, hemorrhage	1 (13%)			
Deep cervical, infiltration cellular, plasma cell	3 (38%)			2 (17%)
Deep cervical, infiltration cellular, histiocyte	3 (38%)			
Mediastinal, hemorrhage				2 (17%)
Mediastinal, infiltration cellular, plasma cell	2 (25%)	1 (13%)	4 (36%)	2 (17%)
Mediastinal, infiltration cellular, histiocyte			1 (9%)	1 (8%)
Pancreatic, hemorrhage		2 (25%)		
Pancreatic, infiltration cellular, histiocyte		3 (38%)		1 (8%)
Pancreatic, pigmentation, hemosiderin		2 (25%)		
Renal, infiltration cellular, histiocyte		1 (13%)		1 (8%)
Renal, pigmentation				1 (8%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Infiltration cellular, plasma cell		1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, histiocyte	50 (100%)	49 (98%)	48 (96%)	49 (98%)
Spleen	(49)	(50)	(50)	(50)
Accessory spleen			1 (2%)	1 (2%)
Autolysis			2 (4%)	
Fibrosis	1 (2%)			1 (2%)
Hematopoietic cell proliferation	47 (96%)	45 (90%)	40 (80%)	45 (90%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	2 (4%)
Infarct	1 (2%)			
Inflammation, granulomatous	1 (2%)	1 (2%)		
Pigmentation, hemosiderin	48 (98%)	50 (100%)	49 (98%)	49 (98%)
Lymphoid follicle, atrophy		5 (10%)		
Red pulp, hyperplasia				1 (2%)
Thymus	(50)	(49)	(46)	(50)
Atrophy	49 (98%)	48 (98%)	44 (96%)	49 (98%)
Cyst				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Galactocele	7 (14%)	3 (6%)	2 (4%)	2 (4%)
Hyperplasia	3 (6%)	4 (8%)	1 (2%)	3 (6%)
Inflammation	1 (2%)	1 (2%)	1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)	1 (2%)
Sebaceous gland, hyperplasia				1 (2%)
Subcutaneous tissue, necrosis			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy				2 (4%)
Skeletal muscle	(1)	(1)	(3)	(1)
Inflammation	1 (100%)	1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Gliosis			1 (2%)	
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	
Hydrocephalus	1 (2%)			
Inflammation	1 (2%)	1 (2%)	1 (2%)	
Mineralization	1 (2%)			
Necrosis		1 (2%)	1 (2%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Inflammation, acute		2 (4%)	1 (2%)	
Inflammation, granulomatous	12 (24%)	5 (10%)	9 (18%)	7 (14%)
Metaplasia, squamous			1 (2%)	
Alveolar epithelium, hyperplasia	18 (36%)	18 (36%)	13 (26%)	15 (30%)
Alveolus, infiltration cellular, histiocyte	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Interstitium, fibrosis			1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Inflammation	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Thrombosis			2 (4%)	
Trachea	(50)	(50)	(50)	(50)
Inflammation		4 (8%)	2 (4%)	1 (2%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Inflammation	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Lens, cataract	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Optic nerve, fibrosis				1 (2%)
Retina, degeneration	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Retina, dysplasia		1 (2%)		
Harderian gland	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid	14 (28%)	10 (20%)	6 (12%)	9 (18%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet			2 (4%)	1 (2%)
Fibrosis	1 (2%)			
Infarct		1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active	1 (2%)			
Nephropathy	47 (94%)	49 (98%)	48 (96%)	49 (98%)
Cortex, inflammation				1 (2%)
Cortex, mineralization	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Medulla, fibrosis	1 (2%)			
Medulla, mineralization	43 (86%)	49 (98%)	49 (98%)	46 (92%)
Pelvis, inflammation	1 (2%)		4 (8%)	2 (4%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Renal tubule, cyst				1 (2%)
Renal tubule, hyperplasia		1 (2%)	1 (2%)	1 (2%)
Renal tubule, pigmentation				1 (2%)
Renal tubule, vacuolization cytoplasmic		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)	1 (2%)	
Inflammation	1 (2%)	1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF BENZOPHENONE

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	5	3	5	2
Natural deaths	1	3	1	3
Survivors				
Terminal sacrifice	44	44	44	45
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(49)	(49)	(49)
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Polyp adenomatous			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Hepatoblastoma		1 (2%)	1 (2%)	3 (6%)
Hepatocellular carcinoma	6 (12%)	5 (10%)	4 (8%)	6 (12%)
Hepatocellular carcinoma, multiple	2 (4%)		2 (4%)	
Hepatocellular adenoma	9 (18%)	7 (14%)	15 (30%)	11 (22%)
Hepatocellular adenoma, multiple	2 (4%)	8 (16%)	8 (16%)	12 (24%)
Ito cell tumor benign			1 (2%)	
Mesentery		(2)	(8)	(5)
Fat, hemangiosarcoma, metastatic, spleen		1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	2 (4%)	3 (6%)	
Squamous cell papilloma, multiple		1 (2%)		
Tongue		(1)		
Squamous cell carcinoma		1 (100%)		
Tooth	(20)	(31)	(33)	(21)
Odontoma	1 (5%)			1 (5%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, adventitia, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adrenal medulla	(50)	(50)	(50)	(50)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
None				
Genital System				
Prostate	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)		1 (2%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, skeletal muscle	1 (2%)			
Schwannoma malignant, metastatic, skin	1 (2%)			
Lymph node	(1)	(1)	(3)	(5)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (100%)			
Lymph node, mandibular	(48)	(50)	(49)	(47)
Lymph node, mesenteric	(49)	(50)	(49)	(48)
Spleen	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Thymus	(46)	(48)	(46)	(47)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(49)	(50)	(50)	(50)
Schwannoma malignant, metastatic, skin	1 (2%)			
Skeletal muscle	(1)	(1)	(2)	
Hemangiosarcoma	1 (100%)			
Hemangiosarcoma, metastatic, spleen		1 (100%)		
Squamous cell carcinoma, metastatic, stomach, forestomach			1 (50%)	
Nervous System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	9 (18%)	4 (8%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)	1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)		2 (4%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Mediastinum, alveolus, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Special Senses System				
Harderian gland	(50)	(50)	(50)	(50)
Adenoma	6 (12%)	6 (12%)	4 (8%)	4 (8%)
Carcinoma	1 (2%)	1 (2%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Lymphoma malignant	2 (4%)		2 (4%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	38	30	34	35
Total primary neoplasms	52	46	52	52
Total animals with benign neoplasms	27	23	30	27
Total benign neoplasms	34	36	40	39
Total animals with malignant neoplasms	17	10	11	13
Total malignant neoplasms	18	10	12	13
Total animals with metastatic neoplasms	6	5	3	3
Total metastatic neoplasms	11	7	3	3

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 6 3	5 4 0	6 5 2	6 7 9	6 9 0	7 0 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 0 4 6	0 0 4 4	0 0 4 0	0 0 1 9	0 0 3 8	0 0 3 3	0 0 0 2	0 0 0 9	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 1 6	0 0 1 7	0 0 1 8	0 0 3 3	0 0 3 5	0 0 4 7	0 0 4 8	0 0 4 9	0 0 1	0 0 1 5	0 1 0	0 2 0	0 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X							X				X			X					X				
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma						X								X							X	X			
Hepatocellular adenoma, multiple								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+							+							+		+	+	+					+
Odontoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aorta, adventitia, alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Hemangiosarcoma				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 8	0 2 9	0 4 0	0 4 1	0 4 3	0 5 0	0 0 6	0 0 7	0 0 8	0 1 1	0 1 6	0 2 0	0 3 1	0 3 2	0 3 4	0 3 6	0 3 7	0 3 9	0 4 2	0 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma										X																6
Hepatocellular carcinoma, multiple						X																	X			2
Hepatocellular adenoma		X			X									X										X	X	9
Hepatocellular adenoma, multiple							X																			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+		+		+	+			+	+	+				+		+	+			+		+	+		20
Odontoma																								X		1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Aorta, adventitia, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X																					1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 6 3	5 4 0	6 5 2	6 7 9	6 9 0	7 0 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 4 6	0 4 4	0 4 4	0 1 9	0 1 8	0 0 3	0 0 2	0 0 9	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 3 3	0 3 5	0 4 7	0 4 8	0 4 9	0 0 1	0 0 5	0 1 0	0 2 0	0 2 1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skeletal muscle			X																							
Schwannoma malignant, metastatic, skin	X																									
Lymph node				+																						
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				X																						
Lymph node, mandibular	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																						
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, histiocytic sarcoma																										X
Subcutaneous tissue, schwannoma, malignant	X																									
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, skin	X																									
Skeletal muscle			+																							
Hemangiosarcoma			X																							
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																							
Spinal cord			+																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 8	0 2 9	0 4 0	0 4 1	0 4 3	0 5 0	0 0 6	0 0 7	0 0 8	0 1 1	0 2 6	0 3 0	0 3 1	0 3 2	0 3 4	0 3 6	0 3 7	0 3 9	0 4 2	0 4 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, skeletal muscle																										1
Schwannoma malignant, metastatic, skin																										1
Lymph node																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X									1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	46
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, schwannoma, malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, skin																										1
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 8	0 2 9	0 4 0	0 4 1	0 4 3	0 5 0	0 6	0 0 7	0 8	0 1 1	0 1 6	0 2 0	0 3 1	0 3 2	0 3 4	0 3 6	0 3 7	0 3 9	0 4 2	0 4 5	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X			X	X						X									10
Alveolar/bronchiolar adenoma, multiple					X															X							4
Alveolar/bronchiolar carcinoma									X																		2
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver																											2
Mediastinum, alveolus, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X		X												6
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant																					X						2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 4	0 7 7	0 8 1	0 8 4	0 9 6	0 9 7	0 9 8	0 9 9	0 5 4	0 5 8	0 6 2	0 6 5	0 6 6	0 7 0	0 7 5	0 7 9	0 8 0	0 8 2	0 8 3	0 8 6	0 8 9	0 9 0	0 9 3	0 9 4	0 9 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic, spleen																										1
Hepatoblastoma												X														1
Hepatocellular carcinoma		X																								5
Hepatocellular adenoma	X		X																X						X	7
Hepatocellular adenoma, multiple								X				X					X						X			8
Mesentery												+														2
Fat, hemangiosarcoma, metastatic, spleen																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X													2
Squamous cell papilloma, multiple																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell carcinoma																										1
Tooth	+	+				+	+	+	+			+	+		+	+	+	+			+	+	+		+	31
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	+	M	+	M	M	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	4 4 9	5 5 4	5 8 5	6 0 6	6 2 0	6 9 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	0 9 1	0 6 4	0 5 9	0 7 6	0 6 7	0 9 2	0 5 5	0 5 6	0 5 7	0 6 0	0 6 1	0 6 8	0 6 9	0 7 2	0 7 8	0 8 5	0 8 7	0 8 8	1 0 0	0 5 1	0 5 2	0 5 3	0 6 3	0 7 1	0 7 3
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Hemangiosarcoma, metastatic, spleen					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X	X		X						X												
Alveolar/bronchiolar adenoma, multiple																X									
Carcinoma, metastatic, harderian gland								X																	
Hepatoblastoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X										X						X					
Carcinoma								X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 4	0 7 7	0 8 1	0 8 4	0 9 6	0 9 7	0 9 8	0 9 9	0 5 4	0 5 8	0 6 2	0 6 5	0 6 6	0 7 0	0 7 5	0 7 9	0 8 0	0 8 2	0 8 3	0 8 6	0 8 9	0 9 0	0 9 3	0 9 4	0 9 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																	X									1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangiosarcoma, metastatic, spleen																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																									+	1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X					X	X			X								X								9
Alveolar/bronchiolar adenoma, multiple													X													2
Carcinoma, metastatic, harderian gland																										1
Hepatoblastoma, metastatic, liver												X														1
Hepatocellular carcinoma, metastatic, liver		X																								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X			X												X							6
Carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	5	8	0	2	9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	4	5	6	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
	9	6	5	7	6	9	5	5	5	6	6	6	6	7	7	8	8	8	0	5	5	5	6	7	7
	1	4	9	6	7	2	5	6	7	0	1	8	9	2	8	5	7	8	0	1	2	3	3	1	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 7 4	0 7 7	0 8 1	0 8 4	0 9 6	0 9 7	0 9 8	0 9 9	0 5 4	0 5 8	0 6 2	0 6 5	0 6 6	0 7 0	0 7 5	0 7 9	0 8 0	0 8 2	0 8 3	0 8 6	0 8 9	0 9 0	0 9 3	0 9 4	0 9 5	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	585	589	671	679	683	722	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731
Carcass ID Number	11219	12124	11218	11442	11339	11550	11001	11006	11009	11010	11200	11225	11241	11549	11003	11005	11008	11011	11112	11113	11116	11222	11223	11226	11229
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous						X																			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma				X															X						
Hepatocellular carcinoma, multiple																		X							
Hepatocellular adenoma	X								X	X		X		X		X			X			X			
Hepatocellular adenoma, multiple				X				X												X					
Ito cell tumor benign																			X						
Mesentery	+			+	+																+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																				
Squamous cell papilloma														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth	+	+	+	+			+	+	+	+	+				+		+	+	+	+		+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												X													
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 3 2	1 3 5	1 3 7	1 4 0	1 4 4	1 4 7	1 4 8	1 0 2	1 0 4	1 0 7	1 1 4	1 1 5	1 1 7	1 2 1	1 2 7	1 2 8	1 3 0	1 3 1	1 3 3	1 3 4	1 3 6	1 3 8	1 4 3	1 4 5	1 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma	X																									1
Hepatocellular carcinoma	X										X															4
Hepatocellular carcinoma, multiple																				X						2
Hepatocellular adenoma								X									X	X	X				X	X	X	15
Hepatocellular adenoma, multiple	X	X					X				X					X										8
Ito cell tumor benign																										1
Mesentery	+						+									+						+				8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Squamous cell papilloma											X						X									3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+		+		+	+			+	+	+					+	+		+		+	+	33
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	5 8 5	5 8 9	6 7 1	6 7 9	6 8 3	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 1 9	1 2 4	1 1 8	1 4 2	1 3 9	1 5 0	1 0 1	1 0 6	1 0 9	1 1 0	1 2 0	1 2 5	1 4 1	1 4 9	1 0 3	1 0 5	1 0 8	1 1 1	1 1 2	1 1 3	1 1 6	1 2 2	1 2 3	1 2 6	1 2 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Squamous cell carcinoma, metastatic, stomach, forestomach					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma								X																	
Hepatocellular carcinoma, metastatic, liver																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X					X																			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 3 2	1 3 5	1 3 7	1 4 0	1 4 4	1 4 7	1 4 8	1 0 2	1 0 4	1 0 7	1 1 4	1 1 5	1 1 7	1 2 1	1 2 7	1 2 8	1 3 0	1 3 1	1 3 3	1 3 4	1 3 6	1 3 8	1 4 3	1 4 5	1 4 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																		+								3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle					+																					2
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																					+					1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X								X												X		4
Alveolar/bronchiolar adenoma, multiple										X			X													2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver											X									X						2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X							X					4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant								X										X								2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 8 5	1 8 7	1 9 0	1 9 3	1 9 5	1 9 9	2 0 0	1 5 5	1 5 6	1 5 8	1 5 9	1 6 1	1 6 4	1 6 7	1 6 8	1 7 2	1 7 3	1 7 5	1 7 8	1 8 2	1 8 3	1 8 6	1 8 9	1 9 1	1 9 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																				X						3
Hepatocellular carcinoma															X		X								X	6
Hepatocellular adenoma	X	X			X										X				X							11
Hepatocellular adenoma, multiple						X												X		X			X	X		12
Mesentery		+								+		+														5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+			+	+					+	+				+		+		+		+			+	21
Odontoma		X																								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	+	M	+	+	M	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

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

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	6/50 (12%)	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted rate[b]	12.4%	12.6%	8.2%	8.3%
Terminal rate[c]	4/44 (9%)	5/44 (11%)	2/44 (5%)	4/45 (9%)
First incidence (days)	652	606	585	730 (T)
Poly-3 test[d]	P=0.258N	P=0.610	P=0.363N	P=0.368N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	7/50 (14%)	4/50 (8%)	4/50 (8%)
Adjusted rate	14.4%	14.7%	8.2%	8.3%
Terminal rate	4/44 (9%)	6/44 (14%)	2/44 (5%)	4/45 (9%)
First incidence (days)	652	606	585	730 (T)
Poly-3 test	P=0.158N	P=0.600	P=0.257N	P=0.261N
Liver: Hepatocellular Adenoma				
Overall rate	11/50 (22%)	15/50 (30%)	23/50 (46%)	23/50 (46%)
Adjusted rate	22.9%	31.5%	46.9%	46.6%
Terminal rate	10/44 (23%)	14/44 (32%)	21/44 (48%)	21/45 (47%)
First incidence (days)	703	606	585	568
Poly-3 test	P=0.006	P=0.239	P=0.010	P=0.011
Liver: Hepatocellular Carcinoma				
Overall rate	8/50 (16%)	5/50 (10%)	6/50 (12%)	6/50 (12%)
Adjusted rate	16.5%	10.3%	12.3%	12.3%
Terminal rate	7/44 (16%)	2/44 (5%)	5/44 (11%)	4/45 (9%)
First incidence (days)	540	449	679	656
Poly-3 test	P=0.396N	P=0.274N	P=0.386N	P=0.381N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	18/50 (36%)	20/50 (40%)	25/50 (50%)	27/50 (54%)
Adjusted rate	37.0%	40.7%	50.9%	54.6%
Terminal rate	16/44 (36%)	16/44 (36%)	23/44 (52%)	24/45 (53%)
First incidence (days)	540	449	585	568
Poly-3 test	P=0.034	P=0.434	P=0.118	P=0.060
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.1%	2.1%	6.1%
Terminal rate	0/44 (0%)	1/44 (2%)	1/44 (2%)	2/45 (4%)
First incidence (days)	—[e]	730 (T)	730 (T)	606
Poly-3 test	P=0.057	P=0.497	P=0.502	P=0.123
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	8/50 (16%)	6/50 (12%)	6/50 (12%)	9/50 (18%)
Adjusted rate	16.5%	12.3%	12.3%	18.2%
Terminal rate	7/44 (16%)	3/44 (7%)	5/44 (11%)	6/45 (13%)
First incidence (days)	540	449	679	606
Poly-3 test	P=0.393	P=0.384N	P=0.386N	P=0.515
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	18/50 (36%)	20/50 (40%)	25/50 (50%)	29/50 (58%)
Adjusted rate	37.0%	40.7%	50.9%	58.1%
Terminal rate	16/44 (36%)	16/44 (36%)	23/44 (52%)	25/45 (56%)
First incidence (days)	540	449	585	568
Poly-3 test	P=0.013	P=0.434	P=0.118	P=0.027

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	14/50 (28%)	11/50 (22%)	6/50 (12%)	9/50 (18%)
Adjusted rate	29.1%	22.9%	12.4%	18.6%
Terminal rate	13/44 (30%)	9/44 (21%)	5/44 (11%)	9/45 (20%)
First incidence (days)	690	606	722	730 (T)
Poly-3 test	P=0.110N	P=0.322N	P=0.036N	P=0.163N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	16/50 (32%)	11/50 (22%)	7/50 (14%)	9/50 (18%)
Adjusted rate	33.2%	22.9%	14.5%	18.6%
Terminal rate	14/44 (32%)	9/44 (21%)	6/44 (14%)	9/45 (20%)
First incidence (days)	679	606	722	730 (T)
Poly-3 test	P=0.057N	P=0.186N	P=0.025N	P=0.078N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	1/50 (2%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.1%	6.4%	6.2%	0.0%
Terminal rate	1/44 (2%)	3/44 (7%)	3/44 (7%)	0/45 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	—
Poly-3 test	P=0.272N	P=0.300	P=0.309	P=0.498N
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rate	2.1%	6.4%	8.2%	0.0%
Terminal rate	1/44 (2%)	3/44 (7%)	3/44 (7%)	0/45 (0%)
First incidence (days)	730 (T)	730 (T)	683	—
Poly-3 test	P=0.304N	P=0.300	P=0.183	P=0.498N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.2%	4.2%	2.1%	0.0%
Terminal rate	1/44 (2%)	1/44 (2%)	1/44 (2%)	0/45 (0%)
First incidence (days)	652	620	730 (T)	—
Poly-3 test	P=0.061N	P=0.507N	P=0.306N	P=0.119N
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.2%	0.0%	4.1%	6.2%
Terminal rate	1/44 (2%)	0/44 (0%)	2/44 (5%)	2/45 (4%)
First incidence (days)	690	—	730 (T)	700
Poly-3 test	P=0.245	P=0.241N	P=0.691N	P=0.505
All Organs: Benign Neoplasms				
Overall rate	27/50 (54%)	23/50 (46%)	30/50 (60%)	27/50 (54%)
Adjusted rate	55.7%	47.9%	61.1%	54.8%
Terminal rate	24/44 (55%)	21/44 (48%)	27/44 (61%)	25/45 (56%)
First incidence (days)	652	606	585	568
Poly-3 test	P=0.446	P=0.285N	P=0.370	P=0.543N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	10/50 (20%)	11/50 (22%)	13/50 (26%)
Adjusted rate	34.0%	20.4%	22.6%	26.3%
Terminal rate	11/44 (25%)	6/44 (14%)	9/44 (21%)	9/45 (20%)
First incidence (days)	463	449	679	606
Poly-3 test	P=0.326N	P=0.097N	P=0.150N	P=0.269N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	38/50 (76%)	30/50 (60%)	34/50 (68%)	35/50 (70%)
Adjusted rate	76.0%	60.6%	69.0%	70.0%
Terminal rate	32/44 (73%)	25/44 (57%)	30/44 (68%)	30/45 (67%)
First incidence (days)	463	449	585	568
Poly-3 test	P=0.463N	P=0.074N	P=0.288N	P=0.327N

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

TABLE C4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Historical Incidence in Feed Controls Given NTP-2000 Diet				
Benzophenone	11/50	8/50	0/50	18/50
Citral	20/100	13/100	0/100	28/100
p p′-Dichlorodiphenyl sulfone	6/50	9/50	0/50	15/50
trans-Cinnamaldehyde	14/100	13/100	0/100	26/100
2-Methylimidazole	7/50	4/50	0/50	10/50
o-Nitrotoluene	18/60	12/60	1/60	28/60
p-Nitrotoluene	14/50	8/50	0/50	20/50
Overall Historical Incidence: Feed Studies				
Total (%)	90/460 (19.6%)	67/460 (14.6%)	1/460 (0.2%)	145/460 (31.5%)
Mean ± standard deviation	20% ± 7.1%	14.9% ± 3.9%	0.2% ± 0.6%	32.4% ± 9.1%
Range	12%-30%	8%-20%	0%-2%	20%-47%
Overall Historical Incidence: All Routes				
Total (%)	398/1,257 (31.7%)	275/1,257 (21.9%)	22/1,257 (1.8%)	607/1,257 (48.3%)
Mean ± standard deviation	33.2% ± 12.1%	22.9% ± 9.4%	1.9% ± 3.4%	50.4% ± 16.1%
Range	12%-63%	8%-46%	0%-13%	20%-85%

[a] Data as of April 19, 2004

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	5	3	5	2
Natural deaths	1	3	1	3
Survivors				
Terminal sacrifice	44	44	44	45
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(49)	(49)	(49)
Cyst			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	4 (8%)	2 (4%)	5 (10%)	
Clear cell focus	2 (4%)	7 (14%)	7 (14%)	12 (24%)
Eosinophilic focus	5 (10%)	8 (16%)	11 (22%)	10 (20%)
Fatty change			1 (2%)	
Fibrosis			1 (2%)	
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Infarct		2 (4%)		1 (2%)
Infiltration cellular, lymphoid	6 (12%)	10 (20%)		4 (8%)
Inflammation, chronic active	33 (66%)	47 (94%)	44 (88%)	42 (84%)
Mixed cell focus	8 (16%)	9 (18%)	15 (30%)	13 (26%)
Tension lipidosis	1 (2%)	1 (2%)		1 (2%)
Bile duct, cyst		3 (6%)		1 (2%)
Hepatocyte, degeneration, cystic			5 (10%)	30 (60%)
Hepatocyte, multinucleated		41 (82%)	47 (94%)	48 (96%)
Hepatocyte, necrosis	1 (2%)	6 (12%)	8 (16%)	8 (16%)
Hepatocyte, vacuolization cytoplasmic	44 (88%)	45 (90%)	46 (92%)	44 (88%)
Hepatocyte, centrilobular, hypertrophy		44 (88%)	50 (100%)	48 (96%)
Oval cell, hyperplasia			1 (2%)	
Mesentery		(2)	(8)	(5)
Fat, fibrosis		1 (50%)	5 (63%)	1 (20%)
Fat, inflammation, chronic active		1 (50%)	5 (63%)	2 (40%)
Fat, mineralization		1 (50%)	3 (38%)	
Fat, necrosis		1 (50%)	5 (63%)	
Fat, pigmentation		1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Cyst			1 (2%)	2 (4%)
Cytoplasmic alteration	1 (2%)			
Infiltration cellular, lymphoid	14 (28%)	11 (22%)	8 (16%)	8 (16%)
Acinus, atrophy		1 (2%)	1 (2%)	1 (2%)
Acinus, cytoplasmic alteration			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Infiltration cellular, lymphoid	31 (62%)	40 (80%)	40 (80%)	28 (56%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Inflammation, chronic active	1 (2%)	2 (4%)		
Epithelium, cyst		1 (2%)		
Epithelium, hyperkeratosis	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Epithelium, hyperplasia, squamous	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Epithelium, ulcer	1 (2%)	1 (2%)		
Stomach, glandular	(50)	(50)	(50)	(50)
Glands, ectasia	7 (14%)	13 (26%)	18 (36%)	5 (10%)
Glands, mineralization			1 (2%)	1 (2%)
Tooth	(20)	(31)	(33)	(21)
Inflammation, chronic active	1 (5%)		3 (9%)	
Malformation	3 (15%)	1 (3%)	3 (9%)	
Gingiva, inflammation, chronic active	18 (90%)	30 (97%)	32 (97%)	20 (95%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hyperplasia, atypical				1 (2%)
Inflammation, chronic active	3 (6%)	5 (10%)	3 (6%)	3 (6%)
Mineralization	1 (2%)			1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Degeneration, fatty			2 (4%)	
Hyperplasia	7 (14%)	10 (20%)	9 (18%)	6 (12%)
Hypertrophy	26 (52%)	22 (44%)	24 (48%)	18 (36%)
Inflammation, chronic active			1 (2%)	
Necrosis		1 (2%)		
Subcapsular, hyperplasia	50 (100%)	46 (92%)	46 (92%)	47 (94%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		
Pituitary gland	(48)	(49)	(50)	(50)
Pars distalis, cyst	7 (15%)	5 (10%)	5 (10%)	4 (8%)
Pars distalis, hyperplasia	1 (2%)	1 (2%)		
Pars nervosa, cyst		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid			1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)			
Follicle, cyst	2 (4%)			1 (2%)
Follicle, degeneration	12 (24%)	9 (18%)	6 (12%)	6 (12%)
Follicular cell, hyperplasia			1 (2%)	1 (2%)
General Body System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Degeneration		1 (2%)		
Granuloma sperm	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, lymphoid	32 (64%)	27 (54%)	30 (60%)	31 (62%)
Mineralization			4 (8%)	
Spermatocele			1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)
Inflammation, chronic active	21 (42%)	23 (46%)	25 (50%)	32 (64%)
Duct, ectasia	20 (40%)	15 (30%)	15 (30%)	28 (56%)
Prostate	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid	32 (64%)	43 (86%)	46 (92%)	28 (56%)
Inflammation, chronic active	1 (2%)			
Artery, inflammation, chronic active		1 (2%)		1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Artery, inflammation, chronic active	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Mineralization		1 (2%)	4 (8%)	12 (24%)
Germinal epithelium, degeneration		3 (6%)	1 (2%)	2 (4%)
Rete testes, cyst		1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Myeloid cell, hyperplasia			1 (2%)	
Lymph node	(1)	(1)	(3)	(5)
Deep cervical, hyperplasia, lymphoid			1 (33%)	
Mediastinal, hyperplasia, lymphoid		1 (100%)	1 (33%)	
Mediastinal, infiltration cellular, histiocyte	1 (100%)			
Mediastinal, inflammation, granulomatous				1 (20%)
Lymph node, mandibular	(48)	(50)	(49)	(47)
Hyperplasia, lymphoid	5 (10%)	1 (2%)	6 (12%)	5 (11%)
Lymph node, mesenteric	(49)	(50)	(49)	(48)
Hyperplasia, lymphoid	2 (4%)	2 (4%)		2 (4%)
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, granulomatous				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Hematopoietic cell proliferation	11 (22%)	7 (14%)	9 (18%)	14 (28%)
Lymphoid follicle, hyperplasia, lymphoid	17 (34%)	31 (62%)	34 (68%)	32 (64%)
Thymus	(46)	(48)	(46)	(47)
Atrophy	12 (26%)	9 (19%)	6 (13%)	5 (11%)
Cyst	16 (35%)	25 (52%)	20 (43%)	20 (43%)
Ectopic parathyroid gland	2 (4%)			
Ectopic thyroid			1 (2%)	
Infiltration cellular, histiocyte	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Inflammation, granulomatous	1 (2%)			
Mineralization				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Musculoskeletal System				
None				
Nervous System				
Spinal cord	(1)	(1)	(1)	
Degeneration	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid	32 (64%)	38 (76%)	47 (94%)	36 (72%)
Inflammation, chronic active	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)	
Necrosis	1 (2%)			
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	6 (12%)	7 (14%)	8 (16%)	4 (8%)
Alveolus, infiltration cellular, histiocyte	7 (14%)	1 (2%)	1 (2%)	3 (6%)
Mediastinum, inflammation, suppurative			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Inflammation, chronic active	2 (4%)		1 (2%)	2 (4%)
Inflammation, focal, suppurative				1 (2%)
Inflammation, suppurative			1 (2%)	
Nasolacrimal duct, inflammation, chronic active			2 (4%)	1 (2%)
Olfactory epithelium, degeneration	1 (2%)			
Olfactory epithelium, metaplasia		2 (4%)	2 (4%)	24 (48%)
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Anterior chamber, iris, inflammation, suppurative		1 (2%)		
Cornea, inflammation, chronic active		1 (2%)	2 (4%)	1 (2%)
Harderian gland	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Infiltration cellular, lymphoid	37 (74%)	33 (66%)	24 (48%)	29 (58%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Mineralization				1 (2%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Infiltration cellular, lymphoid	44 (88%)	44 (88%)	45 (90%)	45 (90%)
Inflammation, chronic active		1 (2%)	2 (4%)	
Metaplasia, osseous	4 (8%)	2 (4%)	1 (2%)	8 (16%)
Mineralization	49 (98%)	50 (100%)	50 (100%)	50 (100%)
Necrosis			1 (2%)	
Nephropathy	49 (98%)	48 (96%)	50 (100%)	50 (100%)
Artery, inflammation, chronic active	1 (2%)	1 (2%)		
Cortex, cyst	4 (8%)	8 (16%)	12 (24%)	22 (44%)
Renal tubule, pigmentation				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid	24 (48%)	24 (48%)	32 (64%)	23 (46%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF BENZOPHENONE

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	4	2	5	6
Natural deaths	6	6	4	12
Survivors				
Terminal sacrifice	40	42	41	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(49)	(50)	(50)	(50)
Histiocytic sarcoma				2 (4%)
Intestine large, colon	(50)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, skeletal muscle				1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Polyp adenomatous	1 (2%)		3 (6%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hemangiosarcoma			1 (2%)	1 (2%)
Hepatocellular carcinoma		1 (2%)		1 (2%)
Hepatocellular adenoma	4 (8%)	3 (6%)	7 (14%)	5 (10%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	3 (6%)	3 (6%)
Histiocytic sarcoma			5 (10%)	3 (6%)
Mast cell tumor malignant			1 (2%)	
Sarcoma stromal, metastatic, uterus	1 (2%)			
Mesentery	(6)	(9)	(11)	(9)
Fat, fibrosarcoma, metastatic, skin				1 (11%)
Fat, fibrous histiocytoma, metastatic, skin				1 (11%)
Fat, hemangiosarcoma, metastatic, skeletal muscle				1 (11%)
Fat, histiocytic sarcoma				2 (22%)
Fat, sarcoma stromal, metastatic, uterus	1 (17%)			
Oral mucosa		(2)		
Gingival, mast cell tumor malignant		1 (50%)		
Pharyngeal, squamous cell papilloma		1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma				2 (4%)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	1 (2%)		2 (4%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Alimentary System (continued)				
Stomach, glandular	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma				1 (2%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Aorta, fibrous histiocytoma, metastatic, skin				1 (2%)
Aorta, histiocytic sarcoma				1 (2%)
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Hemangiosarcoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin				1 (2%)
Histiocytic sarcoma				3 (6%)
Subcapsular, adenoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma benign	1 (2%)	1 (2%)		2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Parathyroid gland	(42)	(41)	(40)	(40)
Pituitary gland	(50)	(50)	(49)	(47)
Pars distalis, adenoma	2 (4%)		2 (4%)	3 (6%)
Pars distalis, histiocytic sarcoma				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma		1 (2%)	2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Ovary	(49)	(50)	(50)	(50)
Cystadenoma	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma			2 (4%)	3 (6%)
Bilateral, granulosa cell tumor malignant			1 (2%)	
Bilateral, tubulostromal adenoma	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Genital System (continued)				
Uterus	(49)	(50)	(50)	(50)
Hemangiosarcoma, metastatic, skeletal muscle				1 (2%)
Histiocytic sarcoma			1 (2%)	3 (6%)
Leiomyoma		1 (2%)		
Polyp stromal	3 (6%)			
Polyp stromal, multiple	1 (2%)			
Sarcoma stromal	1 (2%)			
Bilateral, polyp stromal		1 (2%)		
Endometrium, adenoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)		1 (2%)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	2 (4%)
Mast cell tumor malignant			1 (2%)	
Lymph node	(8)	(12)	(11)	(15)
Deep cervical, carcinoma, metastatic, thyroid gland		1 (8%)		
Inguinal, histiocytic sarcoma				1 (7%)
Lumbar, histiocytic sarcoma			1 (9%)	2 (13%)
Mediastinal, carcinoma, metastatic, thyroid gland				1 (7%)
Mediastinal, fibrous histiocytoma, metastatic, skin				1 (7%)
Mediastinal, hemangiosarcoma, metastatic, skeletal muscle				1 (7%)
Mediastinal, histiocytic sarcoma				3 (20%)
Pancreatic, fibrous histiocytoma, metastatic, skin				1 (7%)
Pancreatic, histiocytic sarcoma				1 (7%)
Renal, fibrous histiocytoma, metastatic, skin				1 (7%)
Renal, histiocytic sarcoma			1 (9%)	2 (13%)
Lymph node, mandibular	(50)	(50)	(50)	(49)
Histiocytic sarcoma			3 (6%)	2 (4%)
Mast cell tumor malignant, metastatic, oral mucosa		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(49)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hemangiosarcoma, metastatic, skeletal muscle				1 (2%)
Histiocytic sarcoma			2 (4%)	3 (6%)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hemangioma		1 (2%)		
Hemangiosarcoma, metastatic, bone marrow	1 (2%)			
Histiocytic sarcoma			2 (4%)	3 (6%)
Thymus	(46)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Mast cell tumor malignant			1 (2%)	
Mast cell tumor malignant, metastatic, oral mucosa		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Adenoma			1 (2%)	
Carcinoma	1 (2%)			
Histiocytic sarcoma				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			
Squamous cell carcinoma		1 (2%)		
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		4 (8%)	1 (2%)
Subcutaneous tissue, fibrous histiocytoma				1 (2%)
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, histiocytic sarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)	1 (2%)		
Subcutaneous tissue, schwannoma malignant, multiple		1 (2%)		
Subcutaneous tissue, trichoepithelioma				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Skeletal muscle	(2)	(4)	(2)	(4)
Hemangiosarcoma				1 (25%)
Histiocytic sarcoma				1 (25%)
Sarcoma stromal, metastatic, uterus	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		5 (10%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Carcinoma, metastatic, thyroid gland		1 (2%)		1 (2%)
Carcinoma, metastatic, uncertain primary site			1 (2%)	
Fibrosarcoma, metastatic, skin			1 (2%)	1 (2%)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Granulosa cell tumor malignant, metastatic, ovary			1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, liver				1 (2%)
Hemangiosarcoma, metastatic, skeletal muscle				1 (2%)
Histiocytic sarcoma			5 (10%)	3 (6%)
Osteosarcoma, metastatic, skin	1 (2%)			
Mediastinum, fibrosarcoma, metastatic, skin				1 (2%)
Nose	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Mast cell tumor malignant			1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Harderian gland	(50)	(50)	(50)	(49)
Adenoma	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Carcinoma				1 (2%)
Histiocytic sarcoma				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma			3 (6%)	3 (6%)
Urinary bladder	(50)	(49)	(50)	(50)
Histiocytic sarcoma				3 (6%)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			5 (10%)	3 (6%)
Lymphoma malignant	8 (16%)	9 (18%)	5 (10%)	10 (20%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	25	28	32	30
Total primary neoplasms	34	39	49	45
Total animals with benign neoplasms	15	17	19	19
Total benign neoplasms	18	23	25	24
Total animals with malignant neoplasms	16	13	18	20
Total malignant neoplasms	16	16	24	21
Total animals with metastatic neoplasms	3	2	3	6
Total metastatic neoplasms	10	7	3	31
Total animals with malignant neoplasms of uncertain primary site			1	

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	23404	23505	23609	24401	24402	24403	24408	20002	20008	20009	21012	21019	22020	24400	24404	24405	24407	25070	21013	21118	22022	23323	23326	23327	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																				X						1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X		X								X		X									4
Hepatocellular adenoma, multiple			X																							1
Sarcoma stromal, metastatic, uterus																										1
Mesentery									+				+													6
Fat, sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																X										1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth				+				+		+			+	+		+	+					+			+	21
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma														X												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																	X									1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma										X					X											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	4 1 4	4 5 6	6 0 6	6 0 8	6 1 0	6 1 3	7 0 8	7 0 9	7 0 9	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 2 7	2 1 1	2 0 4	2 4 9	2 2 1	2 2 3	2 3 8	2 1 6	2 4 6	2 2 6	2 0 1	2 0 3	2 0 5	2 0 6	2 0 7	2 1 0	2 1 4	2 1 5	2 1 7	2 2 4	2 2 5	2 2 8	2 2 9	2 3 0	2 3 1
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma							X																		
Bilateral, tubulostromal adenoma																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																X									
Polyp stromal, multiple																									
Sarcoma stromal								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Lymph node	+		+	+		+		+														+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, bone marrow							X																		
Thymus	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Subcutaneous tissue, fibrosarcoma									X																
Subcutaneous tissue, schwannoma, malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus								X																	
Skeletal muscle						+		+																	
Sarcoma stromal, metastatic, uterus								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+																		
Spinal cord							+																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, multiple					X																				
Osteosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 3 4	2 3 5	2 3 9	2 4 1	2 4 2	2 4 3	2 4 8	2 0 2	2 0 8	2 0 9	2 1 2	2 1 9	2 2 0	2 4 0	2 4 4	2 4 5	2 4 7	2 5 0	2 1 3	2 1 8	2 2 2	2 2 3	2 3 3	2 3 6	2 3 7	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										1
Bilateral, tubulostromal adenoma								X																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal								X											X							3
Polyp stromal, multiple																								X		1
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node										+			+													8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, bone marrow																										1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																			X							1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, schwannoma, malignant														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Skeletal muscle																										2
Sarcoma stromal, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, multiple																										1
Osteosarcoma, metastatic, skin																			X							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 0 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	3 1 6	5 2 2	5 6 1	5 9 5	6 4 1	6 8 0	7 0 3	7 0 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 4	2 7 3	2 6 6	2 5 1	2 9 9	2 9 2	2 5 9	2 9 5	2 5 2	2 5 5	2 5 7	2 5 8	2 6 2	2 6 5	2 6 7	2 6 9	2 7 0	2 7 1	2 7 5	2 7 8	2 8 1	2 8 5	2 8 7	2 8 9	2 9 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland			X																						
Hepatocellular carcinoma																			X						
Hepatocellular adenoma						X										X									
Hepatocellular adenoma, multiple																		X							
Mesentery						+	+										+					+			
Oral mucosa										+															
Gingival, mast cell tumor malignant																									
Pharyngeal, squamous cell papilloma										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth					+	+		+	+			+	+	+	+	+	+			+				+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma			X																						
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 9 8	3 0 0	2 5 4	2 5 6	2 6 0	2 6 1	2 6 3	2 6 8	2 7 4	2 7 7	2 7 9	2 8 2	2 8 3	2 8 4	2 8 8	2 9 1	2 9 3	2 9 4	2 9 7	2 5 3	2 7 2	2 7 6	2 8 0	2 8 6	2 9 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Hepatocellular carcinoma																										1
Hepatocellular adenoma		X																								3
Hepatocellular adenoma, multiple																										1
Mesentery						+		+					+									+			+	9
Oral mucosa																									+	2
Gingival, mast cell tumor malignant																									X	1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+	+	+	+	+	+		+		+				+		+	+	+				+	29
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma																										1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	3 1 6	5 2 2	5 6 1	5 9 5	6 4 1	6 8 0	7 0 3	7 0 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 4	2 7 3	2 6 6	2 5 1	2 9 9	2 9 2	2 5 9	2 9 5	2 5 2	2 5 5	2 5 7	2 5 8	2 6 2	2 6 5	2 6 7	2 6 9	2 7 0	2 7 1	2 7 5	2 7 8	2 8 1	2 8 5	2 8 7	2 8 9	2 9 6
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma									X																
Bilateral, polyp stromal																									
Endometrium, adenoma																					X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland			X																						
Lymph node			+			+	+				+	+					+		+			+			+
Deep cervical, carcinoma, metastatic, thyroid gland			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, oral mucosa																									
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																					X				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, oral mucosa																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma					X																				
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, schwannoma, malignant		X																							
Subcutaneous tissue, schwannoma malignant, multiple																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+	+										+							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X																			X					X
Carcinoma, metastatic, thyroid gland			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland			X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	29 8	30 0	25 4	25 6	26 0	26 1	26 3	26 8	27 4	27 7	27 9	28 2	28 3	28 4	28 8	29 1	29 3	29 4	29 7	25 3	27 2	27 6	28 0	28 6	29 0	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma		X																X								3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Bilateral, polyp stromal											X															1
Endometrium, adenoma																										1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Lymph node													+					+					+			12
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, oral mucosa																									X	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, oral mucosa																									X	1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma																					X					1
Subcutaneous tissue, hemangioma											X															1
Subcutaneous tissue, schwannoma, malignant																										1
Subcutaneous tissue, schwannoma malignant, multiple																										1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle		+																								4
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																X					5
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 312 ppm

Number of Days on Study	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 9 8	3 0 0	2 5 4	2 5 6	2 6 0	2 6 1	2 6 3	2 6 8	2 7 4	2 7 7	2 7 9	2 8 2	2 8 3	2 8 4	2 8 8	2 9 1	2 9 3	2 9 4	2 9 7	2 5 3	2 7 2	2 7 6	2 8 0	2 8 6	2 9 0	Total Tissues/ Tumors
Special Senses System																												
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma			X	X																								3
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant				X				X														X			X			9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 0 0 5	3 0 0 8	3 0 0 9	3 1 0 1	3 1 1 1	3 1 1 2	3 1 1 5	3 1 1 7	3 2 2 5	3 2 2 6	3 2 2 7	3 3 3 3	3 3 3 4	3 3 3 7	3 3 3 8	3 4 4 0	3 4 4 2	3 4 4 4	3 4 4 7	3 4 4 8	3 4 4 9	3 2 2 2	3 2 2 3	3 3 3 0	3 3 3 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																							X		X	3
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																			X							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular adenoma					X								X	X		X	X			X		X				7
Hepatocellular adenoma, multiple																			X		X					3
Histiocytic sarcoma											X		X	X		X										5
Mast cell tumor malignant																										1
Mesentery							+								+		+			+		+		+		11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																			X							2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+	+		+		+			+		+		+		+			+			+	+	+	24
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Pars distalis, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma																										2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	204	478	555	634	645	690	700	704	718	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730
Carcass ID Number	33 2	31 8	32 1	33 5	32 9	34 5	30 6	32 8	33 6	30 1	30 2	30 4	30 7	31 3	31 4	31 6	31 9	32 0	32 4	32 9	34 1	34 3	34 6	35 0	30 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma												X													
Histiocytic sarcoma																									
Bilateral, granulosa cell tumor, malignant																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mast cell tumor malignant		X																							
Lymph node		+			+			+	+			+						+							
Lumbar, histiocytic sarcoma																									
Renal, histiocytic sarcoma									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mast cell tumor malignant		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma	X							X										X				X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 0 5	3 0 8	3 0 9	3 1 0	3 1 1	3 1 2	3 1 5	3 1 7	3 2 5	3 2 6	3 2 7	3 3 3	3 3 4	3 3 7	3 3 8	3 4 0	3 4 2	3 4 4	3 4 7	3 4 8	3 4 9	3 2 2	3 2 3	3 3 0	3 3 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																X						X				3
Histiocytic sarcoma														X		X										2
Bilateral, granulosa cell tumor, malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Mast cell tumor malignant																										1
Lymph node	+					+	+						+			+										11
Lumbar, histiocytic sarcoma													X													1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X	X		X										3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma													X			X										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X			X										2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma													X													1
Mast cell tumor malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle												+														2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	2 0 4	4 7 8	5 5 5	6 3 4	6 4 5	6 9 0	7 0 0	7 0 4	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	3 3 2	3 1 8	3 2 1	3 3 5	3 2 9	3 4 5	3 0 6	3 2 8	3 3 6	3 0 1	3 0 2	3 0 4	3 0 7	3 1 3	3 1 4	3 1 6	3 1 9	3 2 0	3 2 4	3 3 9	3 4 1	3 4 3	3 4 6	3 5 0	3 0 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, uncertain primary site																									
Fibrosarcoma, metastatic, skin																		X							
Granulosa cell tumor malignant, metastatic, ovary																						X			
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Mast cell tumor malignant		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X											X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymphoma malignant					X									X											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 625 ppm

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	30505	30058	30059	31010	31011	31012	31015	31017	32025	32026	32027	32033	33034	33037	33038	34040	34042	34044	34047	34048	34049	42232	42233	43030	43031			Total Tissues/ Tumors
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Alveolar/bronchiolar adenoma																			X					X				2
Carcinoma, metastatic, uncertain primary site																								X				1
Fibrosarcoma, metastatic, skin																												1
Granulosa cell tumor, malignant, metastatic, ovary																												1
Histiocytic sarcoma											X		X	X		X												5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Histiocytic sarcoma																												1
Mast cell tumor malignant																												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Special Senses System																												
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Adenoma																												2
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Histiocytic sarcoma													X	X														3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Histiocytic sarcoma											X		X	X		X												5
Lymphoma malignant	X					X										X												5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	3 4 4	4 0 0	4 3 5	4 6 6	5 3 6	6 0 6	6 3 7	6 3 8	6 4 5	6 5 1	6 7 2	6 7 5	6 7 7	7 0 4	7 0 5	7 1 1	7 1 2	7 1 4	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 8 8 4	3 9 7	3 6 3	3 6 6	3 5 3	3 9 1	3 9 5	3 8 0	3 7 3	3 8 9	3 5 2	3 8 8	3 9 2	3 8 3	3 6 5	4 0 0	3 7 5	3 7 1	3 5 6	3 7 2	3 7 6	3 7 7	3 7 8	3 8 1	3 8 6
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skeletal muscle													X											
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin															X									
Hemangiosarcoma						X																		
Hepatocellular carcinoma																	X							
Hepatocellular adenoma			X																		X			
Hepatocellular adenoma, multiple																								
Histiocytic sarcoma										X														
Mesentery						+		+		+		+	+	+	+		+							
Fat, fibrosarcoma, metastatic, skin														X										
Fat, fibrous histiocytoma, metastatic, skin															X									
Fat, hemangiosarcoma, metastatic, skeletal muscle													X											
Fat, histiocytic sarcoma										X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X										
Fibrous histiocytoma, metastatic, skin															X									
Histiocytic sarcoma																								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X										
Fibrous histiocytoma, metastatic, skin															X									
Histiocytic sarcoma																								
Tooth				+				+			+	+	+		+	+				+			+	
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Aorta, fibrous histiocytoma, metastatic, skin															X									
Aorta, histiocytic sarcoma																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, liver						X																		
Histiocytic sarcoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 8 7	3 9 0	3 9 4	3 9 8	3 5 1	3 5 4	3 5 5	3 5 7	3 5 9	3 6 0	3 6 1	3 6 7	3 6 9	3 7 0	3 7 4	3 7 9	3 8 2	3 9 6	3 9 9	3 5 8	3 6 2	3 6 4	3 6 8	3 8 5	3 9 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X								X																2
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skeletal muscle																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma																										1
Hepatocellular adenoma												X				X									X	5
Hepatocellular adenoma, multiple				X									X							X						3
Histiocytic sarcoma		X								X																3
Mesentery		+																								9
Fat, fibrosarcoma, metastatic, skin																										1
Fat, fibrous histiocytoma, metastatic, skin																										1
Fat, hemangiosarcoma, metastatic, skeletal muscle																										1
Fat, histiocytic sarcoma		X																								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma		X								X																2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma		X																								1
Tooth		+		+		+	+	+						+	+				+		+			+	+	20
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Aorta, fibrous histiocytoma, metastatic, skin																										1
Aorta, histiocytic sarcoma										X																1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, liver																										1
Histiocytic sarcoma		X																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	3 4 4	4 0 0	4 3 5	4 6 6	5 3 6	6 0 6	6 3 7	6 3 8	6 4 5	6 5 1	6 7 2	6 7 5	6 7 7	7 0 4	7 0 5	7 1 1	7 1 2	7 1 4	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 8 8 4	3 9 7	3 6 3	3 6 6	3 5 3	3 9 1	3 9 5	3 8 0	3 7 3	3 8 9	3 5 2	3 8 8	3 9 2	3 8 3	3 6 5	4 0 0	3 7 5	3 7 1	3 5 6	3 7 2	3 7 6	3 7 7	3 7 8	3 8 1	3 8 6
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin														X										
Histiocytic sarcoma										X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Parathyroid gland	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars distalis, adenoma											X		X				X							
Pars distalis, histiocytic sarcoma										X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
C-cell, carcinoma									X															
Follicular cell, adenoma					X																			
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X									
Fibrous histiocytoma, metastatic, skin															X									
Histiocytic sarcoma										X														
Oviduct																				+	+			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, skeletal muscle													X											
Histiocytic sarcoma										X														
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland									X															
Histiocytic sarcoma																								
Lymph node			+	+		+		+	+	+		+	+		+	+			+					
Inguinal, histiocytic sarcoma																								
Lumbar, histiocytic sarcoma																								
Mediastinal, carcinoma, metastatic, thyroid gland									X															
Mediastinal, fibrous histiocytoma, metastatic, skin															X									
Mediastinal, hemangiosarcoma, metastatic, skeletal muscle													X											
Mediastinal, histiocytic sarcoma										X														
Pancreatic, fibrous histiocytoma, metastatic, skin															X									
Pancreatic, histiocytic sarcoma																								
Renal, fibrous histiocytoma, metastatic, skin															X									
Renal, histiocytic sarcoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 8 7	3 9 0	3 9 4	3 9 8	3 5 1	3 5 4	3 5 5	3 5 7	3 5 9	3 6 0	3 6 1	3 6 7	3 6 9	3 7 0	3 7 4	3 7 9	3 8 2	3 9 6	3 9 9	3 5 8	3 6 2	3 6 4	3 6 8	3 8 5	3 9 3	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma		X								X																3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign														X												2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X															1
Parathyroid gland	M	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Pars distalis, adenoma																										3
Pars distalis, histiocytic sarcoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma														X												2
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma		X								X																3
Oviduct															+											3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, skeletal muscle																										1
Histiocytic sarcoma		X								X																3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Histiocytic sarcoma		X								X																2
Lymph node		+								+				+		+										15
Inguinal, histiocytic sarcoma										X																1
Lumbar, histiocytic sarcoma		X								X																2
Mediastinal, carcinoma, metastatic, thyroid gland																										1
Mediastinal, fibrous histiocytoma, metastatic, skin																										1
Mediastinal, hemangiosarcoma, metastatic, skeletal muscle																										1
Mediastinal, histiocytic sarcoma		X								X																3
Pancreatic, fibrous histiocytoma, metastatic, skin																										1
Pancreatic, histiocytic sarcoma		X																								1
Renal, fibrous histiocytoma, metastatic, skin																										1
Renal, histiocytic sarcoma		X								X																2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	3440	4400	4435	4636	5336	6066	6377	6385	6445	6651	6672	6775	6777	7104	7205	7411	7112	7414	7723	7229	7299	7299	7299	7229	7229
Carcass ID Number	3384	3397	3636	3666	3553	3591	3995	3980	3737	3859	3852	3888	3922	3883	3665	4000	3775	3711	3516	3722	3766	3777	3878	3781	3886
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin															X										
Hemangiosarcoma, metastatic, skeletal muscle													X												
Histiocytic sarcoma										X															
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin															X										
Histiocytic sarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma														X											
Subcutaneous tissue, fibrous histiocytoma															X										
Subcutaneous tissue, histiocytic sarcoma																									
Subcutaneous tissue, trichoepithelioma	X																								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+					+					+												
Hemangiosarcoma													X												
Histiocytic sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar adenoma, multiple											X														
Carcinoma, metastatic, thyroid gland									X																
Fibrosarcoma, metastatic, skin														X											
Fibrous histiocytoma, metastatic, skin															X										
Granulosa cell tumor malignant, metastatic, ovary																						X			
Hemangiosarcoma, metastatic, liver						X																			
Hemangiosarcoma, metastatic, skeletal muscle													X												
Histiocytic sarcoma										X															
Mediastinum, fibrosarcoma, metastatic, skin														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 8 7	3 9 0	3 9 4	3 9 8	3 5 1	3 5 4	3 5 5	3 5 7	3 5 9	3 6 0	3 6 1	3 6 7	3 6 9	3 7 0	3 7 4	3 7 9	3 8 2	3 9 6	3 9 9	3 5 8	3 6 2	3 6 4	3 6 8	3 8 5	3 9 3	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma		X								X																2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hemangiosarcoma, metastatic, skeletal muscle																										1
Histiocytic sarcoma		X								X																3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma		X								X																3
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, histiocytic sarcoma		X																								1
Subcutaneous tissue, trichoepithelioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle		+																								4
Hemangiosarcoma																										1
Histiocytic sarcoma		X																								1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												2
Alveolar/bronchiolar adenoma, multiple																										1
Carcinoma, metastatic, thyroid gland																										1
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, skin																										1
Granulosa cell tumor malignant, metastatic, ovary																										1
Hemangiosarcoma, metastatic, liver																										1
Hemangiosarcoma, metastatic, skeletal muscle																										1
Histiocytic sarcoma		X								X																3
Mediastinum, fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X																								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	3440	4004	4035	4466	5336	6006	6037	6338	6645	6651	6772	6775	6777	7074	7205	7211	7112	7114	7223	7229	7229	7229	7229	7229	7229
Carcass ID Number	3384	3397	3063	3066	3553	3591	3995	3980	3737	3889	3552	3888	3992	3883	3665	4005	3775	3711	3516	3772	3776	3777	3778	3781	3886
Special Senses System																									
Ear															+			+							
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X				X																
Carcinoma																				X					
Histiocytic sarcoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin															X										
Histiocytic sarcoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant			X					X	X			X				X							X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of Benzophenone: 1,250 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	38 7	39 0	39 4	39 8	35 1	35 4	35 5	35 7	35 9	36 0	36 1	36 7	36 9	37 0	37 4	37 9	38 2	39 6	39 9	35 8	36 2	36 4	36 8	38 5	39 3	Total Tissues/ Tumors
Special Senses System																										
Ear																										2
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						3
Carcinoma																										1
Histiocytic sarcoma		X																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Histiocytic sarcoma		X								X																3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X								X																3
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma		X								X																3
Lymphoma malignant					X							X				X			X							10

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Harderian Gland: Adenoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate[b]	2.2%	6.4%	4.3%	6.8%
Terminal rate[c]	1/40 (3%)	3/42 (7%)	2/41 (5%)	1/31 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	536
Poly-3 test[d]	P=0.281	P=0.307	P=0.501	P=0.288
Harderian Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.2%	6.4%	4.3%	9.0%
Terminal rate	1/40 (3%)	3/42 (7%)	2/41 (5%)	2/31 (7%)
First incidence (days)	729 (T)	729 (T)	729 (T)	536
Poly-3 test	P=0.147	P=0.307	P=0.501	P=0.164
Small Intestine (Duodenum): Adenomatous Polyp				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	0.0%	6.4%	0.0%
Terminal rate	1/40 (3%)	0/42 (0%)	3/41 (7%)	0/31 (0%)
First incidence (days)	729 (T)	—[e]	729 (T)	—
Poly-3 test	P=0.533N	P=0.499N	P=0.307	P=0.514N
Liver: Hepatocellular Adenoma				
Overall rate	5/50 (10%)	4/50 (8%)	10/50 (20%)	8/50 (16%)
Adjusted rate	10.8%	8.5%	21.4%	18.1%
Terminal rate	5/40 (13%)	3/42 (7%)	10/41 (24%)	7/31 (23%)
First incidence (days)	729 (T)	680	729 (T)	435
Poly-3 test	P=0.109	P=0.494N	P=0.131	P=0.243
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	5/50 (10%)	5/50 (10%)	10/50 (20%)	9/50 (18%)
Adjusted rate	10.8%	10.7%	21.4%	20.3%
Terminal rate	5/40 (13%)	4/42 (10%)	10/41 (24%)	7/31 (23%)
First incidence (days)	729 (T)	680	729 (T)	435
Poly-3 test	P=0.081	P=0.624N	P=0.131	P=0.165
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	10.5%	4.3%	6.9%
Terminal rate	0/40 (0%)	4/42 (10%)	2/41 (5%)	1/31 (3%)
First incidence (days)	—	316	729 (T)	672
Poly-3 test	P=0.260	P=0.033	P=0.238	P=0.108
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.1%	10.5%	4.3%	6.9%
Terminal rate	0/40 (0%)	4/42 (10%)	2/41 (5%)	1/31 (3%)
First incidence (days)	610	316	729 (T)	672
Poly-3 test	P=0.396	P=0.105	P=0.498	P=0.280
Ovary: Cystadenoma				
Overall rate	1/49 (2%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.2%	6.4%	6.4%	4.6%
Terminal rate	0/40 (0%)	3/42 (7%)	3/41 (7%)	1/31 (3%)
First incidence (days)	708	729 (T)	729 (T)	705
Poly-3 test	P=0.433	P=0.308	P=0.307	P=0.477

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	2/50 (4%)	0/50 (0%)	2/49 (4%)	3/47 (6%)
Adjusted rate	4.3%	0.0%	4.4%	7.2%
Terminal rate	2/40 (5%)	0/42 (0%)	2/40 (5%)	0/30 (0%)
First incidence (days)	729 (T)	—	729 (T)	672
Poly-3 test	P=0.202	P=0.236N	P=0.687	P=0.451
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	1/50 (2%)
Adjusted rate	2.2%	0.0%	8.4%	2.3%
Terminal rate	0/40 (0%)	0/42 (0%)	2/41 (5%)	0/31 (0%)
First incidence (days)	709	—	204	704
Poly-3 test	P=0.397	P=0.499N	P=0.187	P=0.745
Skin (Subcutaneous Tissue): Fibrous Histiocytoma or Fibrosarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.2%	0.0%	8.4%	4.6%
Terminal rate	0/40 (0%)	0/42 (0%)	2/41 (5%)	0/31 (0%)
First incidence (days)	709	—	204	704
Poly-3 test	P=0.204	P=0.499N	P=0.187	P=0.477
Skin (Subcutaneous Tissue): Fibroma, Fibrous Histiocytoma, or Fibrosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	2.2%	2.1%	8.4%	4.6%
Terminal rate	0/40 (0%)	1/42 (2%)	2/41 (5%)	0/31 (0%)
First incidence (days)	709	729 (T)	204	704
Poly-3 test	P=0.275	P=0.760N	P=0.187	P=0.477
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	8.6%	2.1%	0.0%	0.0%
Terminal rate	4/40 (10%)	1/42 (2%)	0/41 (0%)	0/31 (0%)
First incidence (days)	729 (T)	729 (T)	—	—
Poly-3 test	P=0.019N	P=0.177N	P=0.060N	P=0.070N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	10.7%	2.1%	0.0%	0.0%
Terminal rate	4/40 (10%)	1/42 (2%)	0/41 (0%)	0/31 (0%)
First incidence (days)	709	729 (T)	—	—
Poly-3 test	P=0.008N	P=0.101N	P=0.030N	P=0.037N
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	10.7%	6.9%
Terminal rate	0/40 (0%)	0/42 (0%)	4/41 (10%)	2/31 (7%)
First incidence (days)	—	—[f]	718	651
Poly-3 test	P=0.032		P=0.031	P=0.108
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	9/50 (18%)	5/50 (10%)	10/50 (20%)
Adjusted rate	16.8%	18.9%	10.6%	22.2%
Terminal rate	5/40 (13%)	6/42 (14%)	4/41 (10%)	5/31 (16%)
First incidence (days)	414	522	645	435
Poly-3 test	P=0.352	P=0.499	P=0.286N	P=0.347

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
All Organs: Benign Neoplasms				
Overall rate	15/50 (30%)	17/50 (34%)	19/50 (38%)	19/50 (38%)
Adjusted rate	32.2%	35.5%	40.6%	40.7%
Terminal rate	14/40 (35%)	15/42 (36%)	18/41 (44%)	10/31 (32%)
First incidence (days)	708	316	704	344
Poly-3 test	P=0.214	P=0.451	P=0.264	P=0.261
All Organs: Malignant Neoplasms				
Overall rate	16/50 (32%)	13/50 (26%)	19/50 (38%)	21/50 (42%)
Adjusted rate	33.1%	26.8%	38.8%	45.4%
Terminal rate	9/40 (23%)	8/42 (19%)	13/41 (32%)	10/31 (32%)
First incidence (days)	414	522	204	435
Poly-3 test	P=0.064	P=0.326N	P=0.352	P=0.154
All Organs: Benign or Malignant Neoplasms				
Overall rate	25/50 (50%)	28/50 (56%)	32/50 (64%)	30/50 (60%)
Adjusted rate	51.7%	56.6%	65.4%	62.5%
Terminal rate	18/40 (45%)	22/42 (52%)	26/41 (63%)	16/31 (52%)
First incidence (days)	414	316	204	344
Poly-3 test	P=0.145	P=0.387	P=0.119	P=0.191

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

TABLE D4
Historical Incidence of Histiocytic Sarcoma in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence in Feed Controls Given NTP-2000 Diet	
Benzophenone	0/50
Citral	0/99
p,p′-Dichlorodiphenyl sulfone	0/50
trans-Cinnamaldehyde	2/100
2-Methylimidazole	0/50
o-Nitrotoluene	0/60
p-Nitrotoluene	0/50
Overall Historical Incidence: Feed Studies	
Total (%)	2/459 (0.4%)
Mean ± standard deviation	0.3% ± 0.8%
Range	0%-2%
Overall Historical Incidence: All Routes	
Total (%)	18/1,258 (1.4%)
Mean ± standard deviation	1.5% ± 2.2%
Range	0%-8%

[a] Data as of April 19, 2004

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

	0 ppm	312 ppm	625 ppm	1,250 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	4	2	5	6
Natural deaths	6	6	4	12
Survivors				
Terminal sacrifice	40	42	41	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(49)	(50)	(50)	(50)
Cyst		1 (2%)	1 (2%)	
Infiltration cellular, lymphoid			1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Mineralization			1 (2%)	
Intestine large, colon	(50)	(50)	(50)	(50)
Inflammation, chronic active				1 (2%)
Intestine small, duodenum	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Intestine small, jejunum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid		3 (6%)		1 (2%)
Intestine small, ileum	(50)	(50)	(50)	(50)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)		1 (2%)	4 (8%)
Basophilic focus	3 (6%)		1 (2%)	2 (4%)
Clear cell focus	3 (6%)	2 (4%)	4 (8%)	4 (8%)
Eosinophilic focus	2 (4%)	2 (4%)	7 (14%)	7 (14%)
Hematopoietic cell proliferation	18 (36%)	11 (22%)	20 (40%)	19 (38%)
Infarct				1 (2%)
Infiltration cellular, lymphoid	36 (72%)	38 (76%)	35 (70%)	35 (70%)
Inflammation, chronic active	44 (88%)	40 (80%)	41 (82%)	36 (72%)
Mineralization			1 (2%)	
Mixed cell focus	2 (4%)	5 (10%)	3 (6%)	2 (4%)
Tension lipidosis	4 (8%)	8 (16%)	3 (6%)	7 (14%)
Bile duct, hyperplasia	1 (2%)			
Hepatocyte, autolysis				1 (2%)
Hepatocyte, mitotic alteration			1 (2%)	
Hepatocyte, multinucleated				2 (4%)
Hepatocyte, necrosis	3 (6%)	5 (10%)	4 (8%)	
Hepatocyte, vacuolization cytoplasmic	41 (82%)	43 (86%)	39 (78%)	34 (68%)
Hepatocyte, centrilobular, degeneration				1 (2%)
Hepatocyte, centrilobular, hypertrophy		29 (58%)	44 (88%)	37 (74%)
Mesentery	(6)	(9)	(11)	(9)
Fat, fibrosis	1 (17%)	2 (22%)	8 (73%)	4 (44%)
Fat, hemorrhage				1 (11%)
Fat, infiltration cellular, lymphoid			4 (36%)	
Fat, inflammation, chronic active	1 (17%)	3 (33%)	7 (64%)	3 (33%)
Fat, mineralization		1 (11%)	2 (18%)	1 (11%)
Fat, necrosis	1 (17%)	4 (44%)	9 (82%)	4 (44%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)		
Infiltration cellular, lymphoid	20 (40%)	24 (48%)	33 (66%)	18 (36%)
Acinus, atrophy	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Acinus, cytoplasmic alteration		1 (2%)		
Duct, inflammation, chronic active			1 (2%)	
Duct, pigmentation			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid	27 (54%)	34 (68%)	30 (60%)	28 (56%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)			1 (2%)
Epithelium, hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Epithelium, hyperplasia, squamous	1 (2%)	1 (2%)		1 (2%)
Epithelium, ulcer	1 (2%)			1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Epithelium, glands, hyperplasia	1 (2%)			
Glands, ectasia	18 (36%)	16 (32%)	22 (44%)	10 (20%)
Glands, mineralization		3 (6%)		2 (4%)
Tooth	(21)	(29)	(24)	(20)
Malformation			1 (4%)	
Gingiva, inflammation, chronic active	21 (100%)	29 (100%)	24 (100%)	20 (100%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Aorta, mineralization				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy			1 (2%)	
Hyperplasia, atypical			1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	
Mineralization			1 (2%)	
Necrosis	1 (2%)			
Valve, inflammation, chronic active	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage				1 (2%)
Hyperplasia	2 (4%)			
Hypertrophy	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)			
Mineralization				1 (2%)
Necrosis		1 (2%)		1 (2%)
Subcapsular, hyperplasia	49 (98%)	49 (98%)	49 (98%)	49 (100%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia			2 (4%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	1 (2%)		
Parathyroid gland	(42)	(41)	(40)	(40)
Cyst			3 (8%)	1 (3%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(49)	(47)
Pars distalis, angiectasis	2 (4%)	4 (8%)	5 (10%)	3 (6%)
Pars distalis, cyst	5 (10%)	3 (6%)	2 (4%)	
Pars distalis, hyperplasia	14 (28%)	14 (28%)	13 (27%)	3 (6%)
Pars distalis, hypertrophy			1 (2%)	
Pars distalis, pigmentation			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular, lymphoid		1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic active		1 (2%)	2 (4%)	
C-cell, hyperplasia				1 (2%)
Follicle, cyst		1 (2%)		
Follicle, degeneration	17 (34%)	19 (38%)	12 (24%)	9 (18%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(50)	(50)
Inflammation, chronic active	8 (16%)	1 (2%)		2 (4%)
Duct, cyst	1 (2%)			
Ovary	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		
Atrophy	48 (98%)	48 (96%)	46 (92%)	45 (90%)
Cyst	22 (45%)	17 (34%)	17 (34%)	14 (28%)
Hemorrhage	2 (4%)	5 (10%)	3 (6%)	4 (8%)
Infiltration cellular, lymphoid				1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	
Mineralization		4 (8%)	2 (4%)	
Pigmentation	6 (12%)	2 (4%)	3 (6%)	1 (2%)
Uterus	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)		1 (2%)	
Inflammation, chronic active	5 (10%)	4 (8%)	2 (4%)	2 (4%)
Endometrium, hyperplasia, cystic	47 (96%)	45 (90%)	44 (88%)	43 (86%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myelofibrosis	18 (36%)	30 (60%)	20 (40%)	26 (52%)
Myeloid cell, hyperplasia	1 (2%)			
Lymph node	(8)	(12)	(11)	(15)
Lumbar, hyperplasia, lymphoid	1 (13%)	1 (8%)		2 (13%)
Mediastinal, atrophy	1 (13%)			
Mediastinal, hyperplasia, lymphoid	2 (25%)	5 (42%)	4 (36%)	4 (27%)
Mediastinal, infiltration cellular, histiocyte	1 (13%)			
Mediastinal, inflammation, chronic active	1 (13%)			
Pancreatic, hyperplasia, lymphoid			2 (18%)	1 (7%)
Pancreatic, pigmentation			1 (9%)	
Renal, hemorrhage		1 (8%)		1 (7%)
Renal, hyperplasia, lymphoid		3 (25%)		1 (7%)
Lymph node, mandibular	(50)	(50)	(50)	(49)
Hyperplasia, lymphoid	4 (8%)	20 (40%)	12 (24%)	9 (18%)
Lymph node, mesenteric	(50)	(49)	(49)	(50)
Hyperplasia, lymphoid	6 (12%)	12 (24%)	6 (12%)	4 (8%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Hematopoietic System (continued)				
Spleen	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation	16 (32%)	35 (70%)	32 (64%)	27 (54%)
Hemorrhage				2 (4%)
Inflammation, chronic active				1 (2%)
Necrosis				1 (2%)
Lymphoid follicle, hyperplasia, lymphoid	24 (48%)	36 (72%)	37 (74%)	22 (44%)
Thymus	(46)	(50)	(50)	(50)
Atrophy	8 (17%)	7 (14%)	3 (6%)	13 (26%)
Cyst	23 (50%)	35 (70%)	31 (62%)	24 (48%)
Ectopic parathyroid gland	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		8 (16%)	5 (10%)	2 (4%)
Infiltration cellular, mast cell			1 (2%)	
Inflammation, chronic active	1 (2%)			
Thymocyte, necrosis		1 (2%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosis		1 (2%)		
Subcutaneous tissue, infiltration cellular, lymphoid		4 (8%)	1 (2%)	
Subcutaneous tissue, infiltration cellular, polymorphonuclear	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Maxilla, fracture				1 (2%)
Skeletal muscle	(2)	(4)	(2)	(4)
Infiltration cellular, lymphoid		3 (75%)	2 (100%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				2 (4%)
Infiltration cellular, lymphoid		1 (2%)	2 (4%)	
Inflammation, chronic active				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Infiltration cellular, lymphoid	33 (66%)	44 (88%)	44 (88%)	35 (70%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Metaplasia, osseous				1 (2%)
Pigmentation				2 (4%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Alveolus, hemorrhage	2 (4%)			3 (6%)
Alveolus, infiltration cellular, histiocyte	1 (2%)			2 (4%)
Mediastinum, inflammation, chronic active	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)			
Olfactory epithelium, metaplasia				39 (78%)
Trachea	(50)	(50)	(50)	(50)
Glands, cyst		1 (2%)		
Glands, inflammation, chronic active		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm	312 ppm	625 ppm	1,250 ppm
Special Senses System				
Eye	(50)	(50)	(50)	(50)
Atrophy	2 (4%)			
Lens, cataract			1 (2%)	
Harderian gland	(50)	(50)	(50)	(49)
Hyperplasia		3 (6%)	3 (6%)	1 (2%)
Infiltration cellular, lymphoid	29 (58%)	27 (54%)	27 (54%)	23 (47%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet			1 (2%)	1 (2%)
Atrophy	1 (2%)			
Glomerulosclerosis				1 (2%)
Hydronephrosis	2 (4%)			1 (2%)
Infarct	4 (8%)	1 (2%)	3 (6%)	3 (6%)
Infiltration cellular, lymphoid	41 (82%)	45 (90%)	43 (86%)	39 (78%)
Inflammation, chronic active	1 (2%)			
Metaplasia, osseous	1 (2%)	2 (4%)	4 (8%)	2 (4%)
Mineralization	15 (30%)	31 (62%)	36 (72%)	49 (98%)
Nephropathy	21 (42%)	33 (66%)	31 (62%)	30 (60%)
Artery, inflammation, chronic active	1 (2%)			1 (2%)
Cortex, cyst		1 (2%)		
Renal tubule, pigmentation	1 (2%)	1 (2%)	1 (2%)	
Urinary bladder	(50)	(49)	(50)	(50)
Infiltration cellular, lymphoid	37 (74%)	38 (78%)	40 (80%)	39 (78%)
Inflammation, chronic active				1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Benzophenone was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of benzophenone. The high dose was limited by toxicity. All trials were repeated.

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

MOUSE BONE MARROW MICRONUCLEUS TEST PROTOCOL

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by benzophenone exposure. For benzophenone, the limiting factor was toxicity. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male mice were injected intraperitoneally three times at 24-hour intervals with benzophenone dissolved in corn oil. Vehicle control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dosed group is less than or equal to 0.025 divided by the number of dosed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 14-week toxicity study (NTP, 2000), peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in each of five animals per exposure group. In addition, the percentage of PCEs in a population of 1,000 erythrocytes was determined as a measure of bone marrow toxicity.

The results were tabulated as described for PCEs in the bone marrow micronucleus test. Results of the 14-week studies were accepted without repeat tests because additional test data could not be obtained.

EVALUATION PROTOCOL

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

RESULTS

Benzophenone showed no evidence of mutagenicity *in vitro* or *in vivo*. Benzophenone (1 to 1,000 µg/plate) did not induce mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat or hamster liver metabolic activation enzymes (Table E1; Mortelmans *et al*., 1986). Intraperitoneal injections of 200 to 500 mg benzophenone/kg body weight (three injections at 24-hour intervals) did not induce micronuclei in bone marrow PCEs of male B6C3F_1 mice (Table E2). A small increase in the frequency of micronucleated PCEs was noted in the 400 mg/kg group, but this increase was not significant. No increases in the frequencies of micronucleated NCEs were seen in peripheral blood of male or female B6C3F_1 mice administered benzophenone for 14 weeks in feed over a concentration range of 1,250 to 20,000 ppm (Table E3). No significant alterations in the percentage of PCEs among total erythrocytes were noted in either micronucleus test, indicating no toxicity to the bone marrow from benzophenone treatment.

TABLE E1
Mutagenicity of Benzophenone in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	–S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	118 ± 12.3	118 ± 11.7	111 ± 1.8	133 ± 7.2	105 ± 8.5	146 ± 4.4
	1	113 ± 7.4					
	3	107 ± 8.1	125 ± 2.2	95 ± 4.6	130 ± 3.8		
	10	110 ± 10.3	132 ± 7.7	102 ± 7.3	136 ± 4.1	90 ± 6.6	131 ± 4.3
	33	100 ± 6.4	123 ± 2.8	84 ± 3.9	128 ± 10.7	96 ± 4.2	112 ± 11.7
	100	110 ± 4.7	114 ± 9.8	78 ± 6.3	154 ± 7.0	99 ± 7.5	124 ± 1.9
	166		52 ± 7.5[c]				
	333			80 ± 4.1	117 ± 8.7	86 ± 7.0	90 ± 6.6
	1,000					50 ± 6.1[c]	35 ± 10.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		383 ± 14.9	297 ± 16.9	1,784 ± 26.1	2,174 ± 37.4	922 ± 112.2	1,638 ± 60.4
TA1535	0	36 ± 1.9	32 ± 2.3	11 ± 2.1	16 ± 1.8	13 ± 3.5	6 ± 1.2
	1	33 ± 2.5					
	3	37 ± 0.7	30 ± 3.2	9 ± 1.7	9 ± 1.7		
	10	31 ± 0.7	30 ± 1.2	9 ± 1.8	10 ± 2.2	11 ± 2.7	12 ± 3.0
	33	26 ± 5.2	27 ± 2.0	10 ± 2.7	10 ± 1.5	8 ± 0.3	6 ± 3.7
	100	32 ± 3.8	22 ± 5.4	7 ± 0.6	11 ± 3.0	10 ± 2.7	8 ± 3.4
	166		0 ± 0.0[c]				
	333			6 ± 1.5	8 ± 0.9	8 ± 2.7	5 ± 0.3
	1,000					4 ± 1.0	1 ± 0.9[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		395 ± 21.7	404 ± 28.2	492 ± 17.2	691 ± 15.2	211 ± 18.1	535 ± 23.0
TA1537	0	4 ± 0.9	7 ± 0.3	9 ± 0.9	7 ± 0.6	7 ± 0.3	6 ± 1.2
	1	6 ± 2.1					
	3	5 ± 0.7	5 ± 1.8	8 ± 2.3	7 ± 2.4		
	10	4 ± 0.9	7 ± 0.6	5 ± 1.2	8 ± 2.6	6 ± 1.2	5 ± 0.7
	33	6 ± 1.7	6 ± 1.2	7 ± 1.5	8 ± 2.3	6 ± 1.2	13 ± 2.0
	100	4 ± 0.3	5 ± 1.8	7 ± 1.8	8 ± 2.7	8 ± 0.6	8 ± 0.6
	166		2 ± 0.3[c]				
	333			3 ± 1.5	5 ± 1.5	7 ± 0.9	5 ± 1.5
	1,000					4 ± 1.8	3 ± 0.3[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		186 ± 19.4	443 ± 51.6	408 ± 11.7	125 ± 7.3	132 ± 20.3	509 ± 19.9

TABLE E1
Mutagenicity of Benzophenone in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA98	0	98 ± 78.0	13 ± 2.6	36 ± 2.5	32 ± 0.0	23 ± 2.3	31 ± 3.3
	1	19 ± 0.3					
	3	19 ± 3.8	13 ± 4.8	34 ± 3.3	39 ± 1.5		
	10	19 ± 1.9	10 ± 2.4	30 ± 2.8	34 ± 4.5	33 ± 1.3	30 ± 0.7
	33	20 ± 2.3	17 ± 0.9	31 ± 2.7	36 ± 4.2	21 ± 2.4	27 ± 7.5
	100	14 ± 1.9	12 ± 2.2	30 ± 3.2	33 ± 4.4	28 ± 5.5	27 ± 1.2
	166		0 ± 0.0[c]				
	333			23 ± 1.0	15 ± 1.2	25 ± 4.5	14 ± 3.2
	1,000					15 ± 2.1	6 ± 0.3[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		475 ± 5.4	431 ± 38.4	1,629 ± 25.7	1,901 ± 39.4	867 ± 11.9	1,221 ± 9.9

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Mortelmans *et al*. (1986). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Administered Benzophenone by Intraperitoneal Injection[a]

	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	P Value[c]	PCEs[b] (%)
Corn oil[d]		5	1.2 ± 0.41		38.2 ± 2.14
Benzophenone	200	5	1.5 ± 0.32	0.2817	47.9 ± 4.57
	300	5	1.5 ± 0.45	0.2817	39.8 ± 5.37
	400	5	2.2 ± 0.72	0.0430	48.7 ± 3.40
	500	5	1.7 ± 0.37	0.1764	42.0 ± 5.44
			P=0.085[e]		
Cyclophosphamide[f]	25	5	22.4 ± 1.85	0.0000	36.0 ± 2.80

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented by Shelby *et al.* (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error.
[c] Pairwise comparison with the vehicle control. Dosed group values are significant at P=0.006; positive control value is significant at P≤0.05 (ILS, 1990)
[d] Vehicle control
[e] Significance of micronucleated PCEs/1,000 PCEs was tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)
[f] Positive control

TABLE E3
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Administration of Benzophenone in Feed for 14 Weeks[a]

	Dose (ppm)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs[b] (%)
Male					
NTP-2000 Feed[d]		5	0.90 ± 0.48		1.92 ± 0.19
Benzophenone	1,250	5	1.40 ± 0.19	0.1484	2.20 ± 0.23
	2,500	5	0.40 ± 0.19	0.9173	2.20 ± 0.29
	5,000	5	1.30 ± 0.34	0.1968	2.08 ± 0.23
	10,000	5	0.50 ± 0.16	0.8576	2.24 ± 0.21
			P=0.866[e]		
Female					
NTP-2000 Feed		5	0.60 ± 0.24		2.06 ± 0.21
Benzophenone	1,250	5	0.80 ± 0.44	0.2964	2.02 ± 0.23
	2,500	5	0.80 ± 0.34	0.2964	2.00 ± 0.27
	5,000	5	0.30 ± 0.20	0.8414	1.88 ± 0.10
	10,000	5	0.80 ± 0.12	0.2964	2.04 ± 0.18
	20,000	5	0.60 ± 0.29	0.5000	2.26 ± 0.36
			P=0.564		

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by MacGregor *et al.* (1990). NCE=normochromatic erythrocyte, PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison with the vehicle control; significant at P=0.006 (males) or P=0.005 (females) (ILS, 1990)
[d] Untreated control
[e] Significance of micronucleated NCEs/1,000 NCEs was tested by the one-tailed trend test; significant at $P \leq 0.025$ (ILS, 1990)

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization of Benzophenone

Benzophenone was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (10803KG) that was used in the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC) and the study laboratory, Battelle Columbus Operations (Columbus, OH). Reports on analyses performed in support of the benzophenone studies are on file at the National Institute of Environmental Health Sciences.

Lot 10803KG, a white crystal with a geranium- or rose-like odor, was identified as benzophenone by melting point determination; infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy; x-ray crystallography; and low and high resolution mass spectrometry by the analytical chemistry laboratory, and the study laboratory confirmed the identity by infrared spectroscopy. The melting point was within acceptable limits of the theoretical values for benzophenone. All spectra were consistent with the structure and matched reference spectra (NIST Standard Reference Database; *Sadtler*, 1979; *Aldrich*, 1981, 1983, 1985) of benzophenone. Infrared, nuclear magnetic resonance, and mass spectra are presented in Figures F1, F2, and F3.

The moisture content of lot 10803KG was determined at the analytical chemistry laboratory by Karl Fischer titration. The purity of lot 10803KG was determined by capillary gas chromatography using a Hewlett-Packard (Palo Alto, CA) gas chromatograph, a J&W (Folsom, CA) SE-30 (low polarity) or DB-17 (high polarity) (30 m × 0.25 mm ID, 0.25-µm film thickness) column, flame ionization detection, with helium (SE-30) or nitrogen (DB-17) as a carrier gas and a flow rate of 1 mL/minute. The study laboratory confirmed the purity of lot 10803KG by capillary gas chromatography using a similar system (low polarity column).

Karl Fischer titration indicated a moisture content of 0.426% (3.7% RSD). Gas chromatography by the analytical chemistry laboratory indicated one major peak that accounted for 100% of the total peak area with both columns. Major peak comparisons with a frozen reference sample of the same lot by the study laboratory using gas chromatography indicated a purity of 100.6% ± 0.5%. The overall purity of lot 10803KG was determined to be 99% or greater.

To ensure stability, the bulk chemical was stored at approximately 25° C in amber glass bottles sealed with Teflon®-lined lids. Periodic purity reanalyses of the bulk chemical were performed by the study laboratory using gas chromatography similar to the low polarity system described above. No degradation of the bulk chemical was detected.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared at least once a month by mixing benzophenone with feed (Table F1). The benzophenone was ground with a mortar and pestle then sieved through a 40-mesh screen. A premix was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for approximately 15 minutes. Formulations were stored in five-gallon white plastic buckets lined with plastic can liners at approximately 5° C for up to 35 days.

Homogeneity studies of the 312 and 1,250 ppm dose formulations were performed by the analytical chemistry laboratory with a Waters (Milford, MA) high performance liquid chromatography (HPLC) system, a reverse phase DuPont Zorbax C8 (25 cm × 4.6 mm ID) column, a Waters 490 UV detector (254 nm), a mobile phase of 35:65 acetonitrile:water, and a flow rate of 2.0 mL/minute. Stability studies of the 312 ppm dose formulation were

also performed by the analytical chemistry laboratory using the same HPLC system. Homogeneity was confirmed, and stability was confirmed for at least 35 days for dose formulations stored in sealed glass containers protected from light up to 5° C. Under simulated animal room dosing conditions, there were small losses after 3 days and significant losses after 7 days. To confirm these findings, the study laboratory performed simulated animal room stability studies of the 312 and 1,250 ppm dose formulations using an HPLC system similar to that described. Results indicated that twice weekly feeder changes should be acceptable, though there would be a slight decrease in concentration of benzophenone.

Periodic analyses of the dose formulations of benzophenone were conducted by the study laboratory using an HPLC system similar to that described above. During the 2-year studies, the dose formulations were analyzed at least every 11 weeks (Table F2). Of the dose formulations analyzed and used, all 63 for rats and all 60 for mice were within 10% of the target concentrations. Animal room samples of these dose formulations were also analyzed; 11 of 24 animal room samples analyzed for rats and 8 of 48 animal room samples analyzed for mice were within 10% of target concentrations. The decline in benzophenone concentration was not anticipated from animal room simulations with air and light performed during pre-study developmental work. After the decline was observed, additional experiments were performed in which benzophenone feed formulations were spiked with rodent urine and feces. Declines were approximately 5% with light and air and increased to approximately 15% in the presence of urine and feces. Contamination occurs when the animals crawl into or onto the feeders. The problem increases in cages where multiple animals are housed and are worst with female mice. Feeders were changed twice per week during the study to minimize the problem, but some contamination was unavoidable.

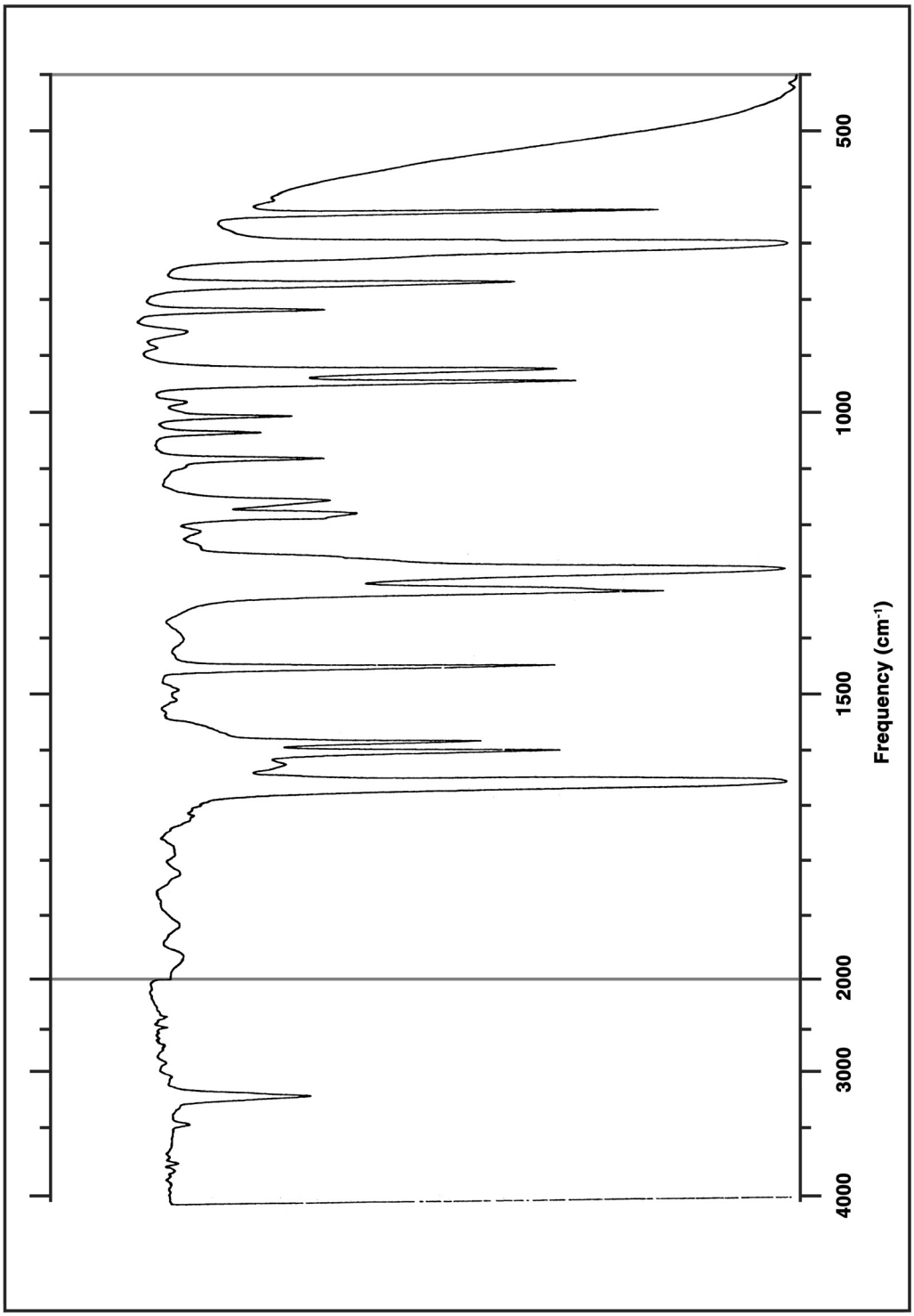


FIGURE F1
Infrared Absorption Spectrum of Benzophenone

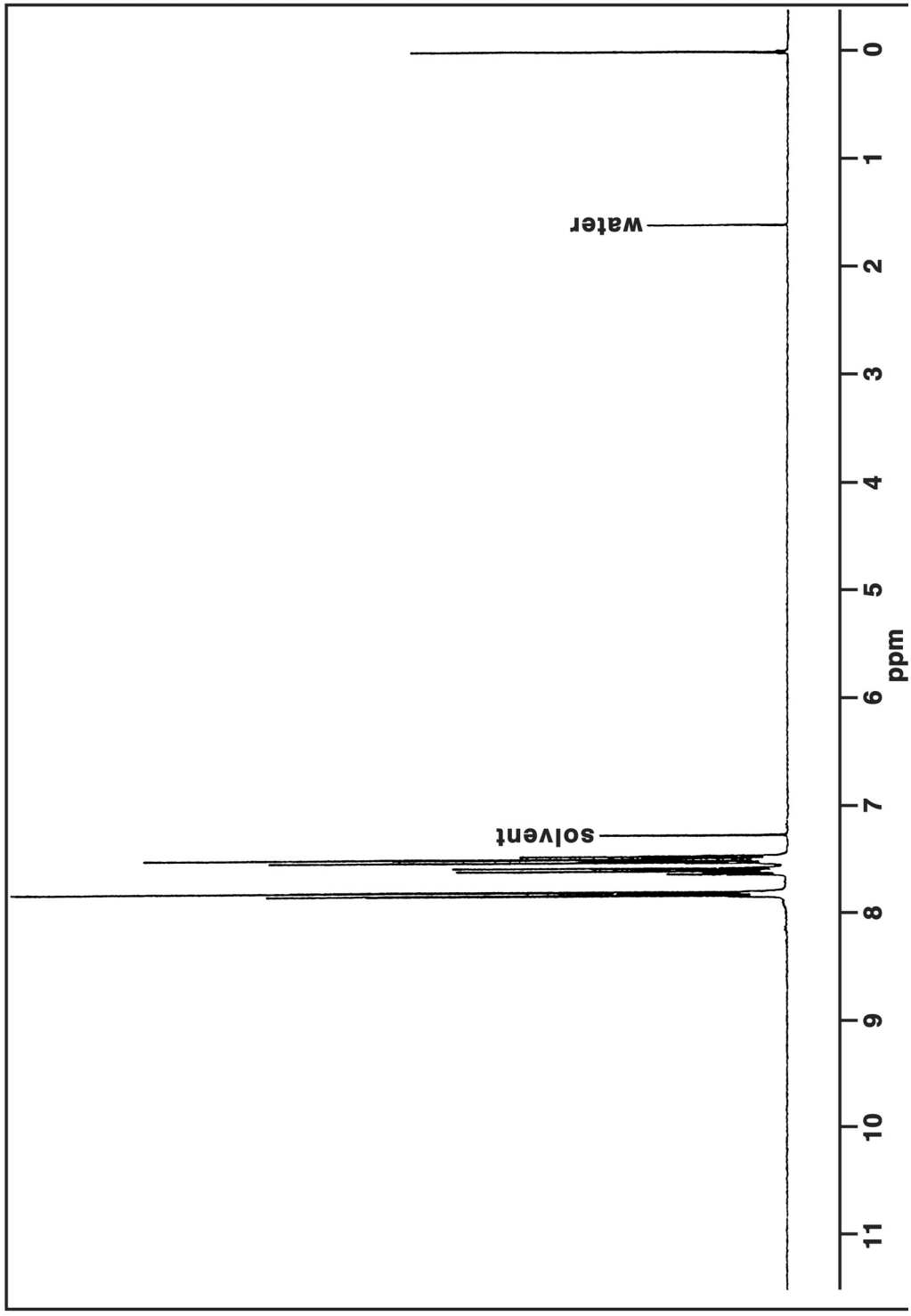


FIGURE F2
Nuclear Magnetic Resonance Spectrum of Benzophenone

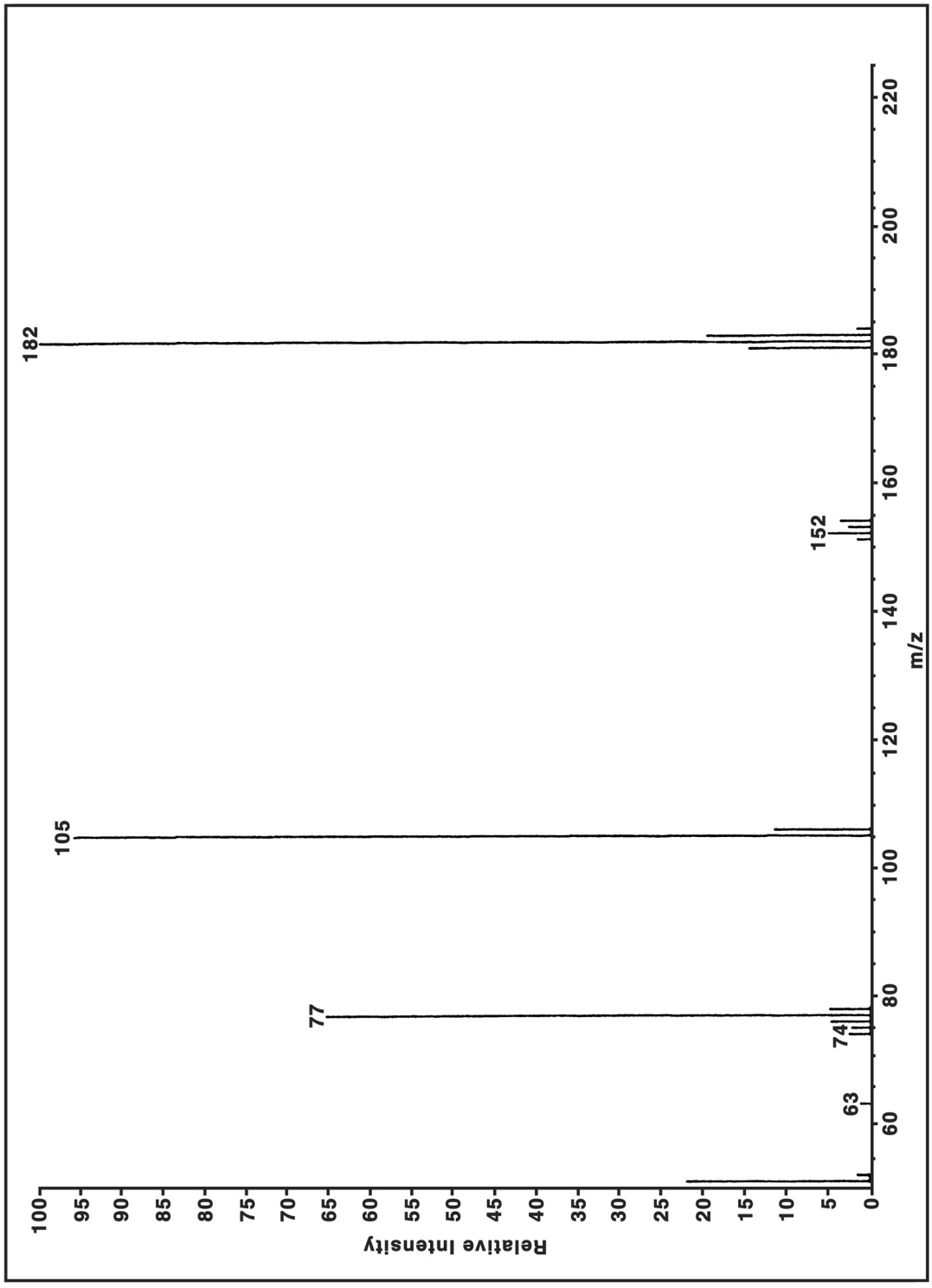


FIGURE F3
Low Resolution Mass Spectrum of Benzophenone

TABLE F1
Preparation and Storage of Dose Formulations in the Feed Studies of Benzophenone

Preparation
Benzophenone was ground with a mortar and pestle then sieved through a 40-mesh screen. A premix was prepared by hand and then blended with additional feed in a Patterson-Kelly twin-shell blender for approximately 15 minutes. Dose formulations were prepared at least once a month.

Chemical Lot Number
10803KG

Maximum Storage Time
35 days

Storage Conditions
Stored in 5-gallon white plastic buckets lined with plastic can liners at approximately 5° C

Study Laboratory
Battelle Columbus Operations (Columbus, OH)

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
August 4, 1999	August 6-7, 1999	312	310.8	0
		625	566.4	–9
		1,250	1,197	–4
August 18, 1999	August 20-21, 1999	312	275.7[b]	–12
		312	302.1	–3
		625	611.5	–2
		625	618.3	–1
		1,250	1,234	–1
		1,250	1,197	–4
	September 23-24, 1999[c]	312	274.9	–12
		625	527.0	–16
		625	569.5	–9
		1,250	1,121	–10
		1,250	1,091	–13
August 27, 1999	August 27, 1999	312	309.0	–1
	September 23-24, 1999[c]	312	274.5	–12
November 4, 1999	November 5-6, 1999	312	314.6	+1
		312	319.5	+2
		625	642.0	+3
		625	607.2	–3
		1,250	1,258	+1
		1,250	1,233	–1
January 20, 2000	January 26, 2000	312	306.5	–2
		312	302.4	–3
		625	608.6	–3
		625	605.3	–3
		1,250	1,232	–1
		1,250	1,241	–1
April 6, 2000	April 10-11, 2000	312	282.4	–9
		312	320.8	+3
		625	601.6	–4
		625	600.9	–4
		1,250	1,193	–5
		1,250	1,181	–6
	May 18-20, 2000[d]	312	290.1	–7
		312	283.7	–9
		625	572.4	–8
		625	785.9	+26
		1,250	1,144	–8
		1,250	1,189	–5

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
June 22, 2000	June 26-27, 2000	312	298.4	–4
		312	305.1	–2
		625	620.7	–1
		625	607.7	–3
		1,250	1,283	+3
		1,250	1,242	–1
September 7, 2000	September 11, 2000	312	307.7	–1
		312	313.9	+1
		625	608.0	–3
		625	621.7	–1
		1,250	1,194	–4
		1,250	1,230	–2
November 21, 2000	November 28-29, 2000	312	315.4	+1
		312	295.6	–5
		625	600.9	–4
		625	620.8	–1
		1,250	1,200	–4
		1,250	1,246	0
	December 28-30, 2000[c]	312	283.4	–9
		312	274.0	–12
		625	572.8	–8
		625	568.6	–9
		1,250	1,108	–11
		1,250	1,103	–12
	December 28-30, 2000[e]	312	309.4	–1
		312	306.8	–2
		625	618.5	–1
		625	607.3	–3
		1,250	1,227	–2
		1,250	1,238	–1
February 8, 2001	February 13-14, 2001	312	304.8	–2
		312	302.2	–3
		625	615.2	–2
		625	620.0	–1
		1,250	1,253	0
		1,250	1,206	–4
April 26, 2001	April 30-May 1, 2001	312	310.1	–1
		312	303.8	–3
		625	622.9	0
		625	630.7	+1
		1,250	1,268	+1
		1,250	1,284	+3

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Rats (continued)				
July 12, 2001	July 17, 2001	312	296.2	–5
		312	296.6	–5
		625	607.7	–3
		625	608.7	–3
		1,250	1,224	–2
		1,250	1,233	–1
	August 17-18, 2001[c]	312	263.1	–16
		312	261.0	–16
		625	534.6	–14
		625	543.1	–13
		1,250	1,146	–8
		1,250	1,261	+1
	August 17-18, 2001[e]	312	306.1	–2
		312	298.5	–4
		625	624.7	0
		625	619.2	–1
		1,250	1,164	–7
		1,250	1,168	–7
Mice				
August 18, 1999	August 20-21, 1999	312	275.7[b]	–12
		312	302.1	–3
		625	611.5	–2
		625	618.3	–1
		1,250	1,234	–1
		1,250	1,197	–4
	September 23-24, 1999[c]	312	274.3	–12
		625	512.4	–18
		625	559.1	–11
		1,250	1,053	–16
		1,250	1,033	–17
	September 23-24, 1999[d]	312	266.5	–15
		625	560.2	–10
		625	540.2	–14
		1,250	1,090	–13
		1,250	1,096	–12
August 27, 1999	August 27, 1999	312	309.0	–1
	September 23-24, 1999[c]	312	253.4	–19
	September 23-24, 1999[d]	312	264.8	–15

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
November 4, 1999	November 5-6, 1999	312	314.6	+1
		312	319.5	+2
		625	642.0	+3
		625	607.2	–3
		1,250	1,258	+1
		1,250	1,233	–1
January 20, 2000	January 26, 2000	312	306.5	–2
		312	302.4	–3
		625	608.6	–3
		625	605.3	–3
		1,250	1,232	–1
		1,250	1,241	–1
April 6, 2000	April 10-11, 2000	312	282.4	–9
		312	320.8	+3
		625	601.6	–4
		625	600.9	–4
		1,250	1,193	–5
		1,250	1,181	–6
	May 18-20, 2000[c]	312	277.2	–11
		312	260.7	–16
		625	554.6	–11
		625	525.1	–16
		1,250	1,096	–12
		1,250	1,086	–13
	May 18-20, 2000[d]	312	285.3	–9
		312	287.4	–8
		625	570.1	–9
		625	572.2	–8
		1,250	1,135	–9
		1,250	1,143	–9
June 22, 2000	June 26-27, 2000	312	298.4	–4
		312	305.1	–2
		625	620.7	–1
		625	607.7	–3
		1,250	1,283	+3
		1,250	1,242	–1
September 7, 2000	September 11, 2000	312	307.7	–1
		312	313.9	+1
		625	608.0	–3
		625	621.7	–1
		1,250	1,194	–4
		1,250	1,230	–2

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
November 21, 2000	November 28-29, 2000	312	315.4	+1
		312	295.6	–5
		625	600.9	–4
		625	620.8	–1
		1,250	1,200	–4
		1,250	1,246	0
	December 28-30, 2000[c]	312	244.2	–22
		312	244.4	–22
		625	519.7	–17
		625	458.3	–27
		1,250	981.1	–22
		1,250	879.8	–30
	December 28-30, 2000[d]	312	276.2	–11
		312	280.9	–10
		625	522.0	–16
		625	534.4	–14
		1,250	1,117	–11
		1,250	1,102	–12
	December 28-30, 2000[e]	312	309.4	–1
		312	306.8	–2
		625	618.5	–1
		625	607.3	–3
		1,250	1,227	–2
		1,250	1,238	–1
February 8, 2001	February 13-14, 2001	312	304.8	–2
		312	302.2	–3
		625	615.2	–2
		625	620.0	–1
		1,250	1,253	0
		1,250	1,206	–4
April 26, 2001	April 30-May 1, 2001	312	310.1	–1
		312	303.8	–3
		625	622.9	0
		625	630.7	+1
		1,250	1,268	+1
		1,250	1,284	+3

TABLE F2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of Benzophenone

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
Mice (continued)				
July 12, 2001	July 17, 2001	312	296.2	–5
		312	296.6	–5
		625	607.7	–3
		625	608.7	–3
		1,250	1,224	–2
		1,250	1,233	–1
	August 17-18, 2001[c]	312	213.0	–32
		312	216.8	–31
		625	425.5	–32
		625	422.2	–32
		1,250	842.1	–33
		1,250	856.6	–31
	August 17-18, 2001[d]	312	264.3	–15
		312	257.1	–18
		625	522.4	–16
		625	541.2	–13
		1,250	1,064	–15
		1,250	1,088	–13
	August 17-18, 2001[e]	312	306.1	–2
		312	298.5	–4
		625	624.7	0
		625	619.2	–1
		1,250	1,164	–7
		1,250	1,168	–7

[a] Results of duplicate analysis
[b] Discarded
[c] Animal room samples; females
[d] Animal room samples; males
[e] Animal room samples; dose formulation storage containers

APPENDIX G
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES OF BENZOPHENONE

TABLE G1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm			625 ppm			1,250 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	17.6	108	17.9	109	51	17.0	109	98	14.6	110	166
2	18.2	144	19.0	148	40	19.0	146	81	21.0	142	185
6	19.5	266	19.4	268	23	20.0	266	47	19.9	264	94
10	18.8	319	18.3	318	18	18.7	319	37	18.8	316	74
14	16.9	352	17.1	352	15	16.5	350	29	18.8	353	67
18	17.2	379	17.4	380	14	17.6	372	30	17.3	372	58
22	18.9	394	18.4	392	15	19.0	388	31	18.5	388	60
26	19.1	416	19.1	413	14	17.8	407	27	17.1	407	53
30	18.3	426	17.8	427	13	18.1	424	27	19.8	423	59
34	17.5	442	17.2	443	12	16.7	438	24	18.3	436	53
38	17.6	453	18.0	455	12	18.7	449	26	18.3	447	51
41	18.5	457	18.6	460	13	18.7	457	26	18.4	450	51
46	18.0	472	17.9	463	12	17.5	468	23	18.9	462	51
50	17.6	478	17.7	476	12	18.2	473	24	17.7	465	48
54	20.3	482	20.0	479	13	19.9	479	26	19.3	466	52
58	17.5	489	17.7	488	11	16.9	486	22	16.2	471	43
62	17.8	494	17.2	493	11	17.6	491	22	17.7	472	47
66	17.1	499	17.3	495	11	17.3	497	22	17.4	472	46
70	16.3	492	17.1	494	11	17.5	485	23	16.9	458	46
74	17.3	498	16.7	491	11	17.2	490	22	16.1	449	45
78	18.5	499	18.6	493	12	17.2	484	22	14.7	436	42
82	18.6	500	18.5	496	12	17.4	479	23	15.8	424	47
86	16.7	502	16.0	494	10	16.7	481	22	14.8	411	45
90	17.1	497	16.8	486	11	16.9	471	22	15.9	384	52
94	15.7	487	16.6	482	11	16.3	463	22	14.4	379	48
98	16.6	478	16.2	478	11	16.0	444	23	14.9	343	54
102	16.5	477	16.3	460	11	15.2	422	23	15.1	306	62
Mean for weeks											
1-13	18.5	209	18.6	211	33	18.7	210	66	18.6	208	130
14-52	18.0	427	17.9	426	13	17.9	423	27	18.3	420	55
53-102	17.4	492	17.3	487	11	17.1	475	23	16.1	421	48

[a] Grams of feed consumed per animal per day
[b] Milligrams of benzophenone consumed per kilogram body weight per day

TABLE G2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm			625 ppm			1,250 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	12.9	101	13.0	101	40	12.9	100	81	11.5	100	144
2	13.2	120	13.1	120	34	13.0	119	68	13.8	118	146
6	12.4	169	12.2	169	23	12.4	165	47	11.3	161	87
10	12.5	189	11.8	186	20	12.0	184	41	11.5	179	80
14	10.9	202	10.0	195	16	10.5	191	34	10.1	187	67
18	11.1	214	10.2	205	15	10.4	201	33	10.0	193	65
22	12.2	219	11.3	210	17	10.8	206	33	10.4	198	65
26	10.8	224	10.6	214	16	10.2	210	30	9.6	202	59
30	10.9	234	10.9	222	15	10.0	216	29	10.0	210	60
34	10.9	241	10.3	227	14	10.1	221	29	9.6	213	57
38	12.2	249	11.4	235	15	11.3	228	31	10.5	219	60
41	11.2	254	11.9	240	15	11.4	233	30	10.9	222	61
46	12.2	264	11.2	249	14	11.2	237	30	10.9	222	61
50	12.6	275	12.1	258	15	11.6	245	30	10.6	231	57
54	12.6	283	12.8	268	15	12.3	253	30	11.3	236	60
58	11.8	290	11.8	273	13	11.4	258	28	10.1	239	53
62	13.2	302	13.5	290	15	13.1	272	30	11.7	250	58
66	13.2	313	12.6	298	13	11.7	279	26	11.3	256	55
70	12.7	318	12.5	306	13	12.4	287	27	11.7	265	55
74	13.4	328	12.6	313	12	12.1	294	26	11.8	272	54
78	12.8	331	12.7	317	13	12.4	300	26	11.8	276	54
82	13.6	338	13.3	324	13	13.2	309	27	12.1	284	53
86	12.8	344	12.3	328	12	12.4	313	25	11.8	287	51
90	13.3	347	12.9	332	12	12.1	312	24	11.2	287	49
94	13.9	346	13.3	333	13	13.0	315	26	11.7	289	51
98	13.1	349	12.8	337	12	12.0	314	24	11.2	291	48
102	12.6	345	13.3	337	12	12.0	313	24	13.0	295	55
Mean for weeks											
1-13	12.7	145	12.5	144	29	12.6	142	59	12.0	139	115
14-52	11.5	237	11.0	226	15	10.7	219	31	10.3	210	61
53-102	13.0	326	12.8	312	13	12.3	294	26	11.6	271	54

[a] Grams of feed consumed per animal per day
[b] Milligrams of benzophenone consumed per kilogram body weight per day

TABLE G3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm			625 ppm			1,250 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	5.0	23.3	5.6	23.1	76	5.2	22.9	143	4.9	23.3	261
2	5.2	23.9	6.5	24.2	84	6.0	23.9	156	5.3	24.0	277
3	4.7	25.2	5.2	24.6	66	5.3	25.0	134	4.9	25.1	245
6	4.9	28.5	5.1	28.7	55	4.9	28.5	107	4.9	28.3	217
10	4.9	32.0	5.2	31.8	52	5.0	31.7	99	5.1	31.3	204
14	5.2	34.9	5.0	34.4	46	5.1	35.3	91	5.0	33.9	183
18	4.8	37.4	5.1	37.5	42	5.0	36.9	85	5.2	35.9	180
22	4.8	38.9	4.8	38.0	39	4.8	38.5	77	5.0	38.3	162
26	5.0	40.9	5.4	40.2	42	5.0	41.0	76	5.1	40.6	158
30	4.5	41.6	4.6	41.3	35	4.4	41.6	66	4.4	41.4	133
34	5.1	43.1	5.2	42.9	38	4.8	41.6	73	5.1	41.9	151
37	5.1	43.6	5.2	43.3	37	5.0	42.9	73	5.1	42.2	151
42	4.8	44.6	4.9	43.9	35	4.9	44.1	69	4.7	43.2	137
46	4.9	45.0	4.7	44.4	33	4.9	44.0	69	4.8	43.6	137
50	4.8	46.0	5.2	45.8	35	5.0	45.0	70	4.9	45.0	137
54	4.8	45.7	5.1	44.9	36	5.0	44.1	71	4.8	44.6	134
58	5.3	45.9	5.4	44.7	37	5.2	44.4	74	5.2	45.6	142
62	5.0	45.9	5.2	44.7	36	4.9	45.4	67	5.1	45.8	138
66	4.9	44.1	5.0	44.8	35	5.0	45.4	69	4.8	45.3	133
70	4.8	43.8	4.9	44.3	34	4.9	44.8	69	4.5	44.7	126
74	4.9	44.0	5.2	45.0	36	5.1	44.9	71	5.1	45.2	141
78	5.1	43.1	5.3	44.1	38	5.1	44.5	71	4.9	43.8	140
84	5.2	40.7	5.3	40.8	41	5.3	40.9	81	5.4	40.4	168
86	5.1	41.7	5.2	41.5	39	5.2	42.2	76	5.2	41.3	156
90	5.0	41.9	5.2	41.7	39	4.9	41.7	74	4.9	41.3	149
94	5.2	41.4	5.1	40.8	39	5.0	41.0	76	5.1	39.8	161
98	4.5	41.2	4.9	39.8	38	4.7	40.3	73	4.9	39.5	155
102	4.6	40.3	4.7	39.5	37	4.6	40.3	71	4.4	38.4	142
Mean for weeks											
1-13	4.9	26.6	5.5	26.5	67	5.3	26.4	128	5.0	26.4	241
14-52	4.9	41.6	5.0	41.2	38	4.9	41.1	75	4.9	40.6	153
53-102	4.9	43.1	5.1	42.8	37	5.0	43.1	73	4.9	42.8	145

[a] Grams of feed consumed per animal per day
[b] Milligrams of benzophenone consumed per kilogram body weight per day

TABLE G4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of Benzophenone

	0 ppm		312 ppm			625 ppm			1,250 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)[b]	Feed (g/day)	Body Weight (g)	Dose (mg/kg)	Feed (g/day)	Body Weight (g)	Dose (mg/kg)
1	3.7	18.8	3.8	18.6	63	3.6	18.6	122	3.5	18.5	233
2	3.8	19.1	3.7	19.5	60	3.8	18.6	128	3.6	19.5	228
6	3.6	22.5	3.5	22.4	48	3.7	22.7	101	3.7	22.8	204
10	3.8	25.0	3.6	25.7	44	3.7	24.0	96	4.0	25.7	197
14	3.8	27.2	4.0	28.4	44	3.9	26.9	92	4.0	28.0	181
18	3.6	29.5	3.9	30.8	39	3.8	30.3	79	4.0	30.3	164
22	4.3	32.8	4.9	33.7	45	4.6	33.3	86	4.5	32.2	173
26	4.1	33.2	4.0	35.1	36	4.3	33.6	80	4.0	33.0	150
30	3.8	35.3	4.2	36.6	36	3.9	35.5	69	3.7	34.4	136
34	3.8	36.5	4.1	38.0	34	3.8	36.9	64	3.8	35.1	134
37	3.8	38.3	4.2	39.7	33	3.9	38.0	64	3.9	36.2	133
42	3.8	39.8	4.1	40.6	31	3.7	39.3	59	3.7	37.2	125
46	3.6	41.2	3.7	42.0	27	3.5	40.0	54	3.4	37.2	114
50	4.0	41.8	3.9	42.9	28	3.8	41.1	58	3.9	37.6	128
54	3.6	43.3	3.8	42.8	28	3.6	41.4	55	4.1	37.2	136
58	4.1	43.7	4.2	43.5	30	3.8	40.2	58	4.1	37.8	135
62	3.9	44.6	3.9	43.5	28	3.9	41.4	59	3.8	37.9	125
66	4.1	44.4	3.8	43.1	27	3.9	41.4	58	3.8	38.5	125
70	4.0	44.4	4.0	43.3	29	4.0	41.7	59	4.0	38.9	130
74	4.2	45.6	4.5	44.2	32	4.4	42.2	65	4.4	39.4	140
78	4.9	46.2	5.0	43.8	36	5.1	41.5	77	4.8	39.5	151
84	3.8	43.5	4.1	41.4	31	4.1	39.5	65	4.5	37.4	149
86	4.3	43.9	4.2	42.0	32	4.7	41.0	71	4.4	37.8	146
90	4.2	44.4	4.0	41.1	31	4.0	40.6	61	4.1	38.4	133
94	3.9	44.4	4.1	41.1	31	4.1	41.1	63	4.2	38.6	136
98	3.8	45.1	4.0	41.3	30	4.2	41.4	63	4.0	38.4	131
102	3.5	43.5	3.8	40.4	29	3.9	40.2	60	3.8	37.2	126
Mean for weeks											
1-13	3.7	21.3	3.7	21.6	54	3.7	21.0	112	3.7	21.6	215
14-52	3.8	35.6	4.1	36.8	35	3.9	35.5	70	3.9	34.1	144
53-102	4.0	44.4	4.1	42.4	30	4.1	41.1	63	4.2	38.2	136

[a] Grams of feed consumed per animal per day
[b] Milligrams of benzophenone consumed per kilogram body weight per day

APPENDIX H
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE H1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE H2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

TABLE H3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.3 ± 0.59	13.4 – 15.5	23
Crude fat (% by weight)	8.3 ± 0.34	7.4 – 9.1	23
Crude fiber (% by weight)	9.0 ± 0.55	7.9 – 10.2	23
Ash (% by weight)	5.2 ± 0.30	4.7 – 6.0	23
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	5,150 ± 1,183	2,960 – 7,560	23
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	9.1 ± 3.41	6.3 – 23.0	23
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	1.070 ± 0.070	0.953 – 1.220	23
Phosphorus (%)	0.609 ± 0.042	0.560 – 0.737	23
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE H4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.21 ± 0.063	0.10 – 0.38	23
Cadmium (ppm)	0.05 ± 0.008	0.04 – 0.07	23
Lead (ppm)	0.08 ± 0.048	0.05 – 0.29	23
Mercury (ppm)	<0.02		23
Selenium (ppm)	0.22 ± 0.052	0.15 – 0.36	23
Aflatoxins (ppb)	<5.00		23
Nitrate nitrogen (ppm)[c]	10.9 ± 2.89	7.86 – 21.1	23
Nitrite nitrogen (ppm)[c]	<0.61		23
BHA (ppm)[d]	<1.0		23
BHT (ppm)[d]	<1.0		23
Aerobic plate count (CFU/g)	14.0 ± 15	10.0 – 80.0	23
Coliform (MPN/g)	2.1 ± 1.8	0.0 – 3.6	23
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[e]	5.3 ± 1.29	2.3 – 7.8	23
N-Nitrosodimethylamine (ppb)[e]	2.3 ± 0.78	1.0 – 3.9	23
N-Nitrosopyrrolidine (ppb)[e]	3.0 ± 0.92	1.3 – 5.3	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl chlorpyrifos	0.180 ± 0.103	0.039 – 0.536	23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.214 ± 0.147	0.020 – 0.515	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

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

APPENDIX I
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

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

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthriditis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	1, 6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	1, 6, 12, and 18 months, study termination

Method and Test	Time of Analysis
MICE	
ELISA	
Ectromelia virus	1, 6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	1, 6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	1, 6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	1, 6, 12, and 18 months, study termination
Mouse adenoma virus-FL	1, 6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	1, 6, 9, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	1, 6, 12, and 18 months, study termination
Reovirus 3	1, 6, 12, and 18 months, study termination
Sendai	1, 6, 12, and 18 months, study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	18 months
Mouse adenoma virus-FL	6 and 12 months, study termination
MCMV (mouse cytomegalovirus)	Study termination
MHV (mouse hepatitis virus)	9 and 12 months
Parvovirus	1, 6, 12, and 18 months, study termination
PVM	6 and 12 months

RESULTS

All serology tests were negative.

APPENDIX J
TOXICOKINETIC STUDIES
IN F344/N RATS AND B6C3F$_1$ MICE

TOXICOKINETIC STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

INTRODUCTION

A single dose of benzophenone was administered by intravenous injection or gavage to male and female F344/N rats and B6C3F$_1$ mice. Concentrations of benzophenone were determined in plasma at timepoints up to 24 hours after dosing. In addition, in the 2-year feed study of benzophenone, plasma samples were analyzed for benzophenone concentrations at 2 weeks and 3, 12, and 18 months in rats and at 12 months in mice. The results were analyzed to establish basic toxicokinetic parameters.

MATERIALS AND METHODS

Single-Dose Studies

Benzophenone was obtained from Aldrich Chemical Company, Inc (Milwaukee, WI) in one lot (10803KG) which was also used in the 2-year studies conducted at Battelle Columbus Laboratories (Columbus, OH). Lot 10803KG was characterized by infrared, ultraviolet/visible, nuclear magnetic resonance, and mass spectroscopy. It was found to be greater than 99% pure by capillary gas chromatography. Dose formulations for the gavage studies were prepared in 0.5% aqueous methylcellulose. Dose formulations for intravenous injection were prepared in Emulphor®:ethanol:deionized distilled water, 10:10:80.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic (Germantown, NY) and were 10 to 11 weeks old at the time of the studies. Animals were quarantined 7 days before use and were housed individually in polycarbonate cages on Ab-Sorb-Dri® cage litter. NTP-2000 feed and water were available *ad libitum*. Room environmental conditions included a temperature range of 69° to 75° F, relative humidity of 40% to 70%, and a 12:12 hour light/dark cycle.

Male and female rats were administered a single intravenous injection of a nominal dose of 2.5 mg benzophenone/kg body weight or a single gavage administration of a nominal dose of 2.5, 5, or 10 mg/kg. The dosing volume was 2 mL/kg by intravenous injection or 5 mL/kg by gavage. Male and female mice were administered a single intravenous injection of a nominal dose of 15 mg/kg or a single gavage administration of a nominal dose of 15, 30, or 60 mg/kg. The dosing volume was 4 mL/kg by intravenous injection or 10 mL/kg by gavage. The actual doses used in the rat and mouse studies (determined by dose analysis) are specified in the tables and figures that summarize the results.

At specified times after dosing, rats were anesthetized with a mixture of carbon dioxide and oxygen, and mice were euthanized with carbon dioxide. Blood samples were collected by retroorbital (rats) or cardiac (mice) puncture from five male and five female rats or one male and one female mouse per timepoint. Generally, two samples were taken from each rat (more than 2 hours apart), one from each eye. The times of blood sample collection after administration of benzophenone are given in Table J1. The samples were collected into heparinized microhematocrit tubes (rats) or heparinized syringes (mice) and the plasma was separated by centrifugation at 1000 × g for 10 minutes and then stored frozen until analysis using a validated method.

For analysis of benzophenone concentrations, 20 µL of a 0.508 mg/mL solution of butyrophenone in acetonitrile was added as an internal standard to a 0.3 mL aliquot of thawed plasma. The samples were mixed and allowed to stand at room temperature for approximately 15 minutes. A sodium chloride solution (0.1 mL of 330 mg sodium chloride/mL water) was added and mixed, followed by the addition of 0.4 mL acetonitrile with additional mixing. After centrifugation, the supernatant was analyzed using a validated high performance liquid chromatography (HPLC) method utilizing a Waters 845 HPLC (Waters Corp., Milford, MA). A Zorbax C8 column

(25 cm × 4.6 mm ID) was eluted with acetonitrile:water (1:1) at 1 mL per minute. Ultraviolet detection was used at 254 nm.

Plasma concentration data were analyzed by noncompartmental modeling techniques using Models 200 and 201 WinNonlin®, Version 1.0 (Scientific Consulting Inc., Cary, NC). These data were also analyzed by compartmental models (WinNonlin®) written to simultaneously solve gavage and intravenous data sets.

2-Year Feed Studies

For determination of plasma concentrations during the 2-year bioassay, groups of 10 male and 10 female rats and mice per dose were designated as the toxicokinetic groups. Blood samples were collected by orbital sinus bleeding from rats at 2 weeks and 3, 12, and 18 months, and from mice at 12 months. Exposure to benzophenone-dosed feed was continued during blood sampling. Samples were taken under CO_2/O_2 anesthesia using heparinized tubes at 1000, 1200, 1400, 1600, and 1800 hours, with n=0 to 2 at each time point. Rats were returned to exposure to benzophenone-dosed feed after each sampling until sacrifice after the 18-month time point. Mice were sacrificed after the 12-month time point. Blood samples were frozen and shipped to the analytical laboratory for analysis.

RESULTS

Rats

Single-Dose Studies

Mean plasma benzophenone concentration versus time data for male and female rats in the intravenous and gavage studies are plotted in Figures J1 and J2, respectively.

Noncompartmental parameter estimates are provided in Table J2. Area under the plasma concentration versus time curve (AUC) appears to be linear with dose for both sexes (AUC/Dose *ca.* 25). For males, bioavailability after a gavage dose ranged from 0.824 to 1.27, with an average value of 1.09. Estimates of elimination rate constants and half-lives (k_{elim} and $t_{½\ elim}$, respectively) for males were similar for the intravenous and low gavage doses (k_{elim} *ca.* 0.00270 min^{-1}; $t_{½\ elim}$ *ca.* 255 min), with slight decreases in k_{elim} and concomitant increases in $t_{½\ elim}$ at the two higher gavage doses (k_{elim} *ca.* 0.00130 min^{-1}; $t_{½\ elim}$ *ca.* 550 min). For female rats, estimates of k_{elim} and $t_{½\ elim}$ were similar for the three gavage doses (k_{elim} *ca.* 0.00150 min^{-1}; $t_{½\ elim}$ *ca.* 485 min). After intravenous administration to females, k_{elim} was slightly higher than after gavage administration, with a concomitant decrease in $t_{½\ elim}$ (k_{elim} = 0.00280 min^{-1}; $t_{½\ elim}$ = 247 min). Bioavailability after a gavage dose ranged from 1.05 to 1.39 in females, with an average value of 1.18. As shown in Figures J1 and J2, there was a great deal of fluctuation in mean plasma benzophenone concentrations at later time points, with secondary increases observed after initial decreases at most of the doses tested, regardless of the route of administration. This variation in concentration in the terminal portion of the curve resulted in extrapolation of up to 31% of the area from the last observed time point to infinity making the accuracy of the AUC and bioavailability estimates uncertain.

Mice

Mean plasma benzophenone concentration versus time data for male and female mice in the intravenous and gavage studies are plotted in Figures J3 and J4, respectively.

Noncompartmental parameter estimates are provided in Table J3; these estimates varied with dose and route of administration. Bioavailability of benzophenone in male and female mice is 50% or less. AUC/Dose, k_{elim}, and $t_{½\ elim}$ are dose dependent in mice, with similar dependency for males and females. As shown in Figures J3 and J4, there was a great deal of fluctuation in plasma benzophenone concentrations at later time points, with clear secondary and even tertiary increases in concentration at all doses tested, regardless of the route of administration.

2-Year Feed Studies

For plasma samples from the 2-year feed studies, AUCs were estimated from the means (n=2) or the individual data points (n=1) using the trapezoidal rule from the time between 1000 and 1800 hours. The results are presented in Table J4. The AUCs are not uniformly dose proportional, although the 12- and 18-month data for rats appear to be dose proportional. The plasma concentrations of benzophenone were significantly higher ($P \leq 0.05$) in female rats and mice compared to males at the same exposure concentration for most of the durations of exposure. Statistical comparisons were by the z-test.

DISCUSSION

The present studies were designed to evaluate the toxicokinetics and estimate the internal dose of benzophenone when administered by intravenous injection or oral gavage to male and female rats and mice. The toxicokinetic studies were conducted to define the oral bioavailability of benzophenone when administered as a bolus gavage dose in aqueous methylcellulose and to establish a dose range over which plasma kinetics are linear.

After intravenous injection of a nominal dose of 2.5 mg benzophenone/kg to male and female rats, benzophenone initially rapidly cleared from the plasma, followed by a slight increase in plasma benzophenone concentration, and a secondary, slower elimination. Secondary maxima in mean plasma benzophenone concentration were observed during the terminal portion of the plasma concentration versus time curve.

After gavage administration of benzophenone to male rats, plasma concentration versus time curves for the three doses were roughly parallel between 200 and 600 minutes. Less well-defined secondary maxima in mean plasma benzophenone concentrations were observed between 5 and 120 minutes after gavage administration of 7.78 mg/kg (nominal dose = 10 mg/kg) to male rats and after gavage administration of 1.88 and 7.68 mg/kg (nominal doses of 2.5 and 10 mg/kg, respectively) to female rats. The similarity of all the intravenous plasma concentration versus time plots suggests that the secondary maxima may be due to enterohepatic recirculation and not artifacts. The characteristic pattern of plasma concentration increases due to enterohepatic recirculation may not be as obvious following gavage administration because the peaks are dampened somewhat by the absorption process, but there are discernable periodic increases in benzophenone concentration in the gavage plasma concentration versus time plots.

Based on the ratios of AUC for intravenous injection and gavage studies, average bioavailability was 1.09 and 1.18 for male and female rats, respectively. Overall, there were no apparent sex-related differences in noncompartmental pharmacokinetic parameter estimates for rats.

After intravenous injection of a nominal dose of 15 mg/kg to male and female mice, benzophenone was initially rapidly cleared from plasma, followed by a slower elimination phase. As with rats, fluctuations in mean plasma benzophenone concentration were observed in mice and were most likely due to enterohepatic recirculation. In mice, the AUCs were supralinear with respect to dose; as the dose was increased, the AUC/dose also increased. In rats, this parameter was more or less constant over the dose range. The nonlinearity in mice may be due to a first-pass effect of liver metabolism restricting the amount of benzophenone that gets into the general circulation. As the dose is increased, the first-pass metabolism becomes saturated. Mice appear to metabolize benzophenone more rapidly than rats; the doses are higher for mice, yet the half-lives and AUCs are smaller. As with rats, there were no obvious sex-related differences in noncompartmental pharmacokinetic parameter estimates for mice.

If benzophenone does undergo enterohepatic recirculation, none of the known metabolites are good candidates for the source of recirculated benzophenone. It may be explained (as shown in the following figure) by reduction to benzhydrol, conjugate formation, biliary excretion, deconjugation by gut flora, reabsorption, and oxidation to benzophenone.

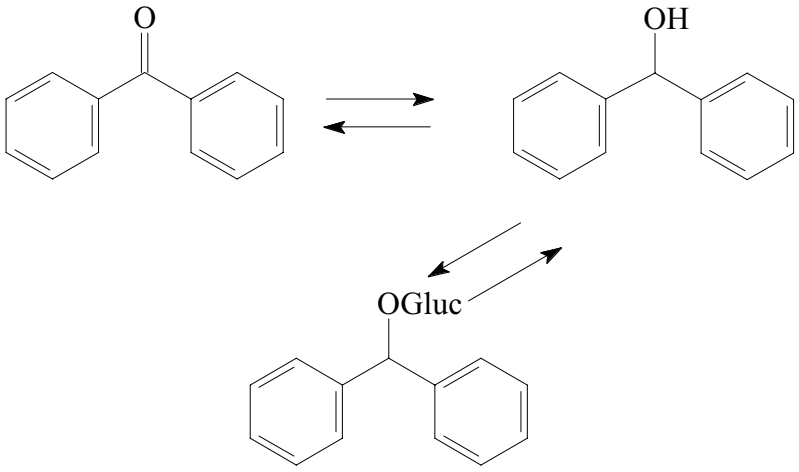


TABLE J1
Blood Collection Times in the Single-Dose Toxicokinetic Studies of Benzophenone

	Route of Administration	Nominal Dose (mg/kg)	Sample Collection Times after Dosing (minutes)
Rats			
	Intravenous	2.5	4, 7, 10, 15, 30, 60, 90, 120, 180, 240, 360, 480, 960
	Gavage	2.5	2.5, 5, 7.5, 10, 15, 30, 60, 120, 180, 360, 480, 600, 960
	Gavage	5	2.5, 5, 7.5, 10, 15, 30, 60, 120, 180, 360, 600, 960, 1440
	Gavage	10	2.5, 5, 7.5, 10, 15, 30, 60, 120, 180, 360, 600, 960, 1440
Mice			
	Intravenous	15	4, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180
	Gavage	15	2.5, 5, 7.5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360
	Gavage	30	2.5, 5, 7.5, 10, 15, 30, 60, 90, 120, 180, 360, 480, 600
	Gavage	60	2.5, 5, 7.5, 10, 15, 30, 60, 120, 180, 360, 600, 960, 1440

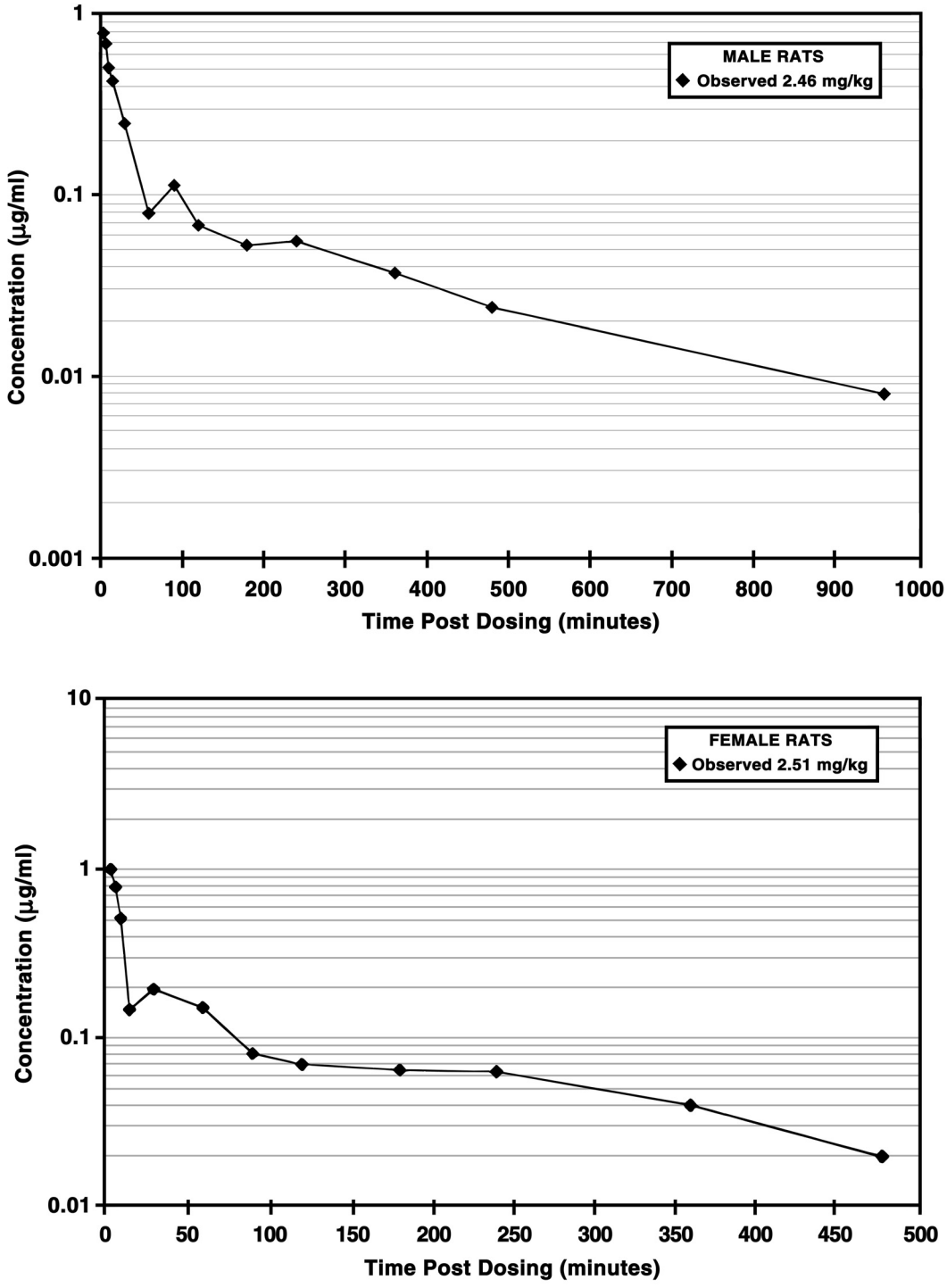
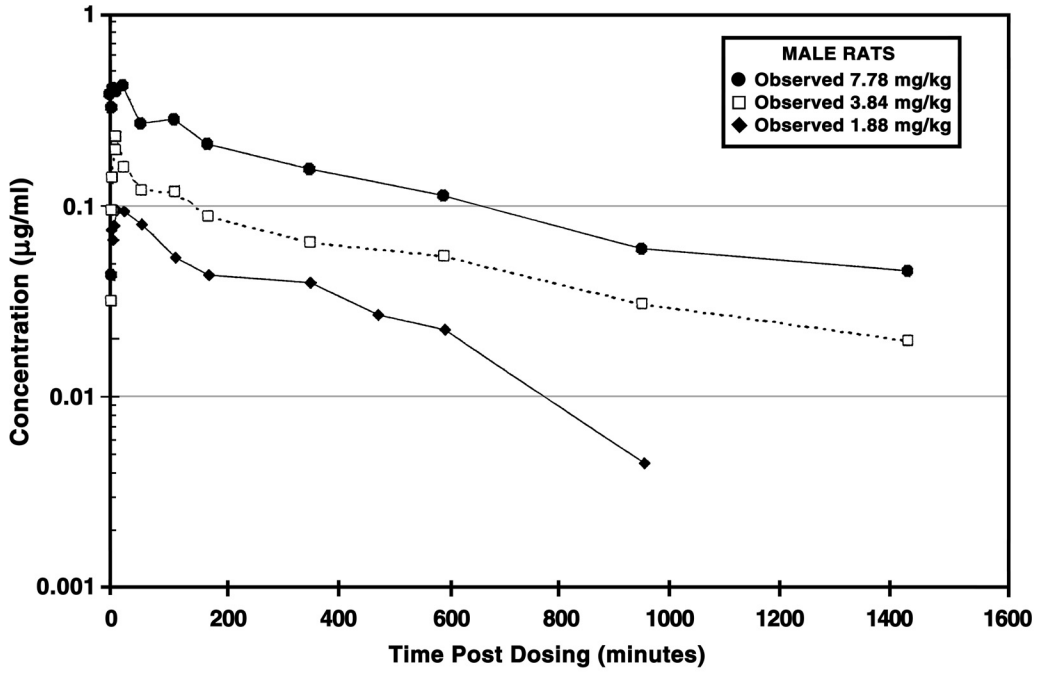


FIGURE J1
Plasma Concentrations of Benzophenone in F344/N Rats after a Single Intravenous Injection of Benzophenone



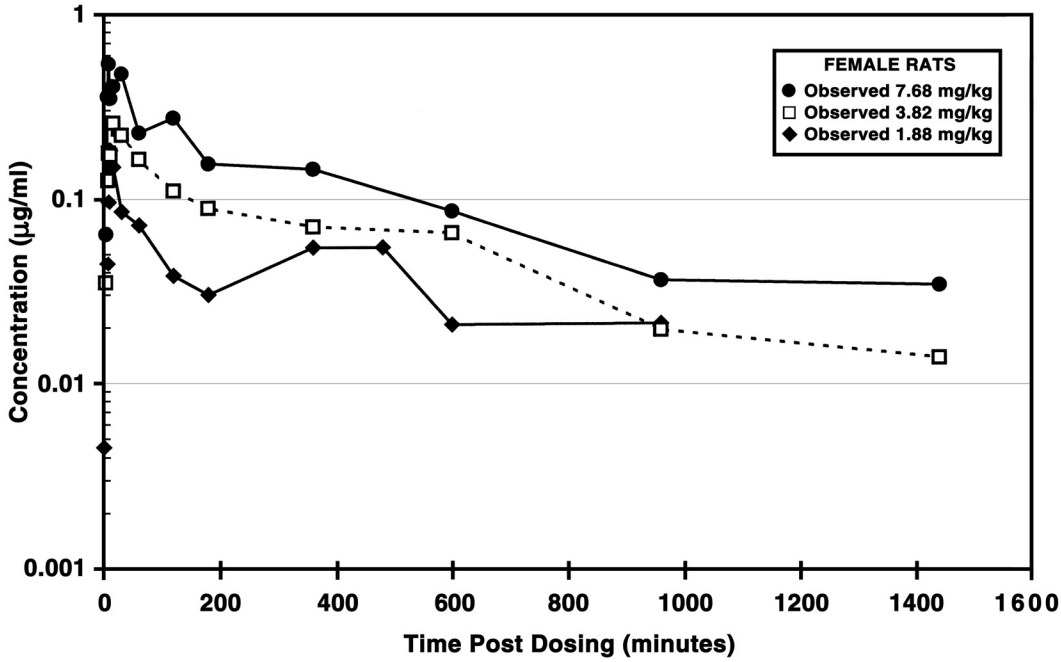
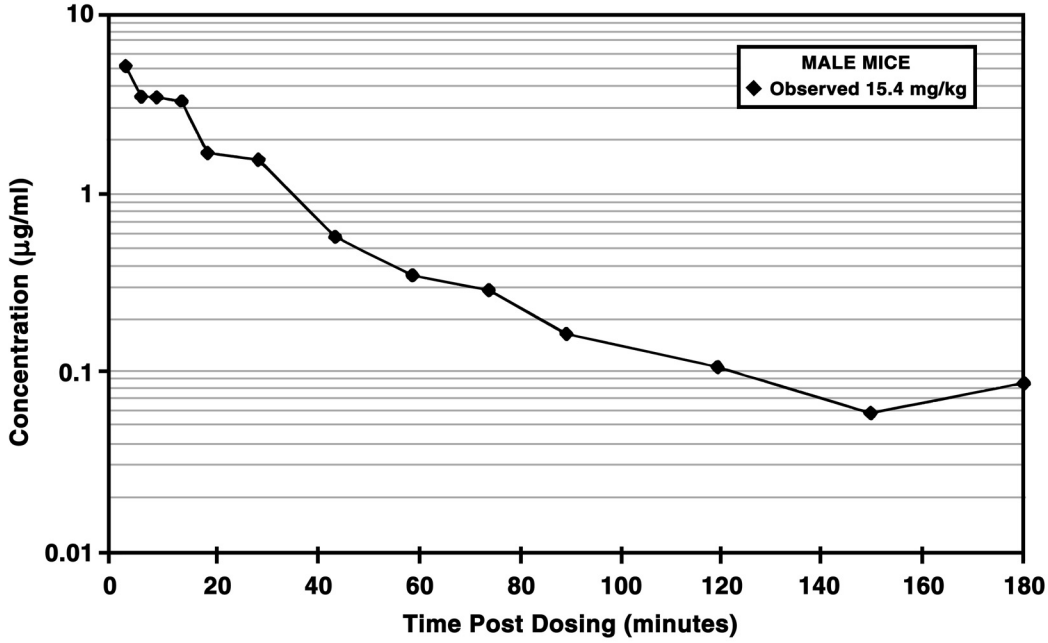


FIGURE J2
Plasma Concentrations of Benzophenone in F344/N Rats after a Single Gavage Dose of Benzophenone

TABLE J2
Noncompartmental Analysis of Plasma Concentration Versus Time Profiles for F344/N Rats Administered Single Intravenous or Gavage Doses of Benzophenone[a]

	Nominal Dose (mg/kg)	Actual Dose[b] (mg/kg)	k_{elim}[c] (min^{-1})	$t_{½\ elim}$[d] (min)	AUC[e] (µg•min/mL)	AUC/ Dose	Bioavailability
Male							
Intravenous	2.5	2.46	0.00260	268	51.9	21.1	—
Gavage	2.5	1.88	0.00280	245	32.7	17.4	0.824
Gavage	5	3.84	0.00120	594	95.6	24.9	1.18
Gavage	10	7.78	0.00140	506	208	26.7	1.27
Female							
Intravenous	2.5	2.51	0.00280	247	51.6	20.6	—
Gavage	2.5	1.88	0.00120	567	53.8	28.6	1.39
Gavage	5	3.82	0.00180	395	86.8	22.7	1.10
Gavage	10	7.68	0.00140	499	166	21.6	1.05

[a] Toxicokinetic parameters were calculated from the plasma concentration-time curves, where each data point represented the mean of five samples
[b] Based on dose analysis
[c] k_{elim}=elimination rate constant
[d] $t_{½\ elim}$=half-life
[e] AUC=area under the plasma concentration versus time curve



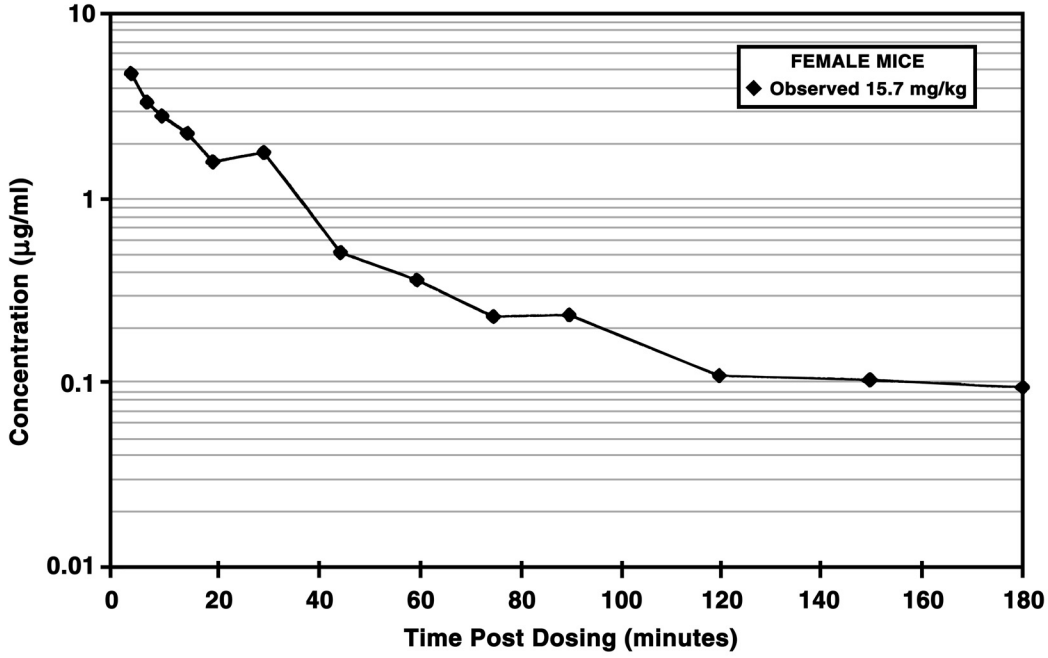


FIGURE J3
Plasma Concentrations of Benzophenone in B6C3F$_1$ Mice after a Single Intravenous Injection of Benzophenone

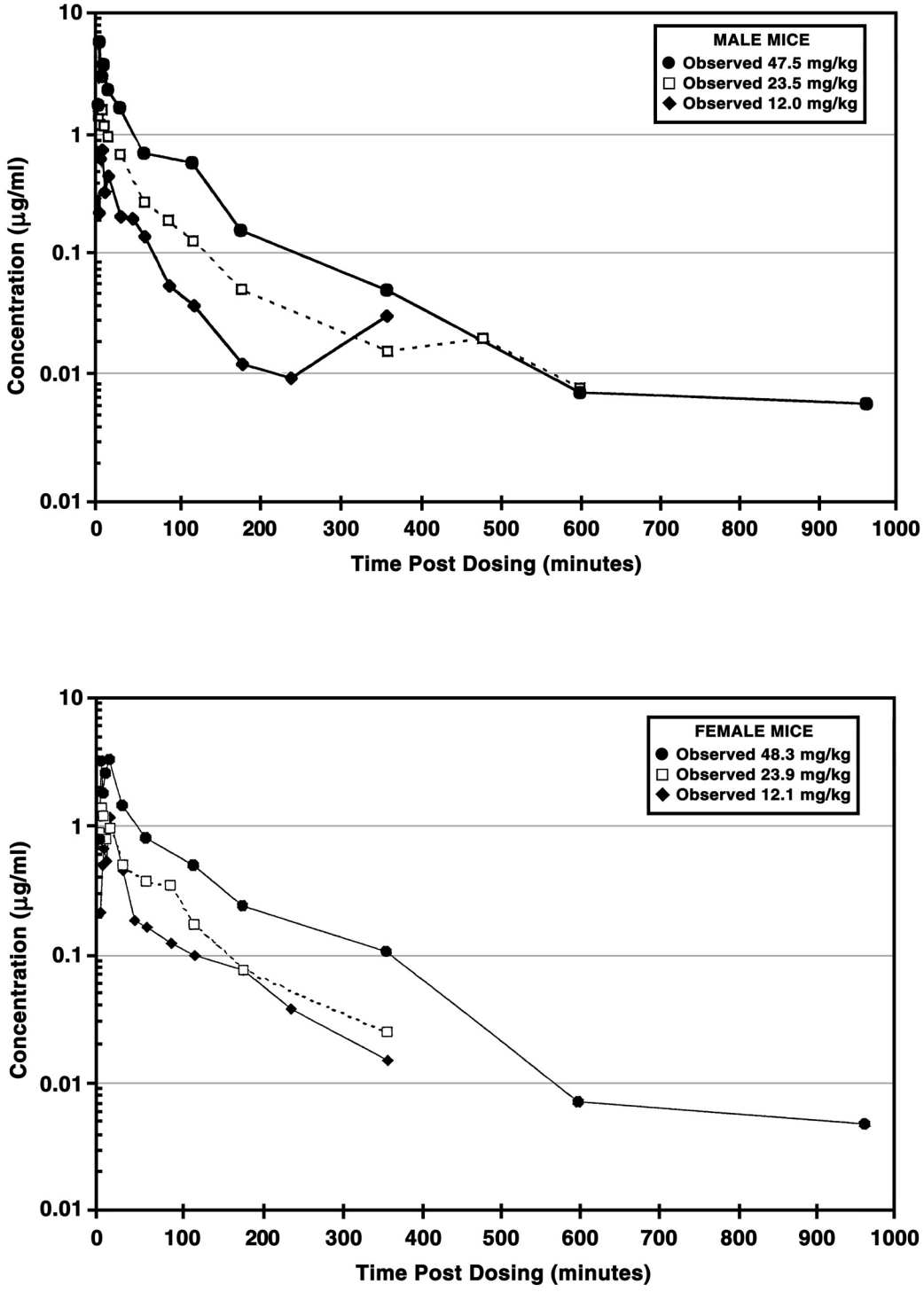


FIGURE J4
Plasma Concentrations of Benzophenone in B6C3F$_1$ Mice after a Single Gavage Dose of Benzophenone

TABLE J3
Noncompartmental Analysis of Plasma Concentration Versus Time Profiles for B6C3F$_1$ Mice Administered Single Intravenous or Gavage Doses of Benzophenone[a]

	Nominal Dose (mg/kg)	Actual Dose[b] (mg/kg)	k_{elim}[c] (min^{-1})	$t_{½\ elim}$[d] (min)	AUC[e] (µg•min/mL)	AUC/ Dose	Bioavailability
Male							
Intravenous	15	15.4	0.0259	26.7	140	9.1	—
Gavage	15	12.0	0.0159	43.6	28.7	2.4	0.263
Gavage	30	23.5	0.00610	113	74.2	3.2	0.347
Gavage	60	47.5	0.00430	160	205	4.3	0.475
Female							
Intravenous	15	15.7	0.0128	54.0	137	8.7	—
Gavage	15	12.1	0.00790	87.5	49.2	4.1	0.468
Gavage	30	23.9	0.00940	73.9	75.9	3.2	0.365
Gavage	60	48.3	0.00640	108	211	4.4	0.501

[a] Toxicokinetic parameters were calculated from the plasma concentration-time curves, where each data point represented one sample
[b] Based on dose analysis
[c] k_{elim}=elimination rate constant
[d] $t_{½\ elim}$=half-life
[e] AUC=area under the plasma concentration versus time curve

Table J4
Area Under the Plasma Concentration Versus Time Curves at 2 Weeks, and 3, 12, and 18 Months in the 2-Year Feed Studies of Benzophenone[a]

	312 ppm	625 ppm	1,250 ppm
Rats			
2 Weeks			
Male	0.981 ± 0.062	1.07 ± 0.07	1.34 ± 0.09
Female	1.181 ± 0.109	1.43 ± 0.08	1.91 ± 0.08
P Value[b]	0.054	0.0004	<0.0001
3 Months			
Male	1.300 ± 0.069	2.16 ± 0.09	2.80 ± 0.06
Female	2.062 ± 0.104	2.47 ± 0.25	5.35 ± 0.40
P Value	<0.0001	0.124	<0.0001
12 Months			
Male	0.597 ± 0.063	1.12 ± 0.07	2.30 ± 0.19
Female	1.939 ± 0.123	3.85 ± 0.46	5.97 ± 0.64
P Value	<0.0001	<0.0001	<0.0001
18 Months			
Male	0.626 ± 0.131	1.45 ± 0.24	3.86 ± 0.14
Female	1.702 ± 0.234	3.46 ± 0.23	6.75 ± 0.63
P Value	<0.0001	<0.0001	<0.0001
Mice			
12 Months			
Male	0.177 ± 0.007	0.085 ± 0.019	0.230 ± 0.082
Female	0.508 ± 0.275	0.287 ± 0.050	0.533 ± 0.129
P Value	0.114	<0.0001	0.024

[a] Data reflect the interval from 1000 to 1800 hours at each analysis and are given in µg • hour/mL as the mean ± standard deviation
[b] P Value from z-test, comparing males and females